JACQUES DESCOTES

HUMAN TOXICOLOGY

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HUMAN TOXICOLOGY

edited by

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This book is dedicated to
Christiane, Jérôme and Aurélie

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Foreword

"*Human Toxicology*" is not an addition to the long list of available textbooks dealing with the clinical toxicity of chemical substances and the management of poisoned patients. There are so many excellent books of this kind that it would have been of little interest to release another one. Instead, this book was designed and edited with two major ideas in mind: firstly, the field of clinical toxicology is changing and an acknowledgement of these changes was warranted; secondly, no comprehensive compilation of recently published case reports of, and clinical studies on, human poisonings is available, which is in sharp contrast to the closely related field of drug-induced side-effects.

Obviously, no or very little information is deliberately provided on the side-effects of drugs in this volume. The management of human poisonings is not dealt with from the viewpoint of emergency medicine as it is generally dealt with in textbooks of clinical toxicology. Instead, more focus has been placed on those issues of recent concern, or on issues which have been poorly reviewed in the past or have not even been included in reference textbooks. This is particularly true for chapters such as "Laboratory diagnosis of poisonings", because it is so important that clinical toxicologists gain a better knowledge of all the available techniques of toxicological analysis, but also a better understanding of the way a sound interpretation of results should be conducted for the benefit of the patient's management, and last but not least, have a comprehensive set of data on the kinetics of the most common pharmaceutical drugs and many chemicals. Other chapters that cover topics otherwise seldom dealt with as comprehensively, include, amongst others, "Food and drug additives", "Anticancer drugs and immunosuppressants", "Solvent abuse" and "Snakes". A glimpse at the newest fields of human toxicology, e.g. "Risk analysis" and "Environmental hazards", has also been provided in the hope that this would be of help to clinical toxicologists more accustomed to the rules of patient management, than to those of epidemiological studies or risk communication.

Because again, "*Human Toxicology*" is not a textbook, there is no consistent format for contributed chapters. Several chapters are long, even very long, but it was thought that the necessary extensive coverage required so many pages and references; other chapters are short because no or very little new informa-

tion has been obtained in the most recent years. As a major goal of the book was to provide recent information on human poisonings, be they acute or chronic, references are consistently less than 10 years old and, in the vast majority of cases, less than 5 years. Despite likely flaws that may be due to the difficulties of starting such a book from scratch — far less easy than updating and revising a previous edition — I hope this volume will prove helpful, and I would like to thank all the contributors who accepted to be involved in this project.

Jacques Descotes
Lyon, Saint Jean d'Avelanne
1996

Human Toxicology, J. Descotes (Ed.)

J. Descotes

Essay: From poison control to poison information from clinical to human toxicology

Even though Orfila paved the way to modern toxicology by using data from human post-mortem examinations as well as the information gained by observing intoxicated animals and humans [1,2], clinical toxicology was actually born in the early 1950s, when Scandinavian doctors introduced the recently discovered concepts of resuscitation to the field of human poisonings [3]. The prognosis of barbiturate comas dropped dramatically from a 30% to a 1% death rate within a few years. With these advances in the treatment of poisonings, trained hospital departments gained wide recognition among physicians as well as the general population and soon received more and more phone queries for advice on the best ways to treat severely poisoned patients. This trend proved to be particularly marked among emergency departments from children's hospitals in the U.S., and with the increasing number of phone calls and the need to respond to this demand, the first Poison Control Centre (PCC) was created in Chicago in 1953. A number of other PCCs were soon started in the U.S., typically in children's hospitals. The trend was somewhat different in Europe as there were fewer pediatricians than in the U.S. at that time, and adult emergency departments, as in Fernand Widal hospital, Paris (in 1959), hosted a PCC. The number of PCCs increased very quickly in the 1960s; among many others, at Helsinski (1961), Lyon (1961), Oslo (1961), Berlin (1963), Brussels (1964), and Zurich (1966), and this led to the creation of associations of Poison Control Centres, as in the U.S. (1957) and in Europe (1964).

Interestingly, the structure of PCCs differed and still differs widely from one country to another: in the U.S., trained nurses answer to phone calls from anyone in the population whatever his background, while in the U.K., health officers only answer phone calls received from medical doctors. In France, as in most European and overseas countries, answers to phone calls received from anyone are given by trained medical doctors. In some countries, networks of PCCs were established, as in the U.S. and the U.K., and to some extent in France, Brazil, Venezuela and Italy. Other countries, partly because of a smaller population size, preferred national centres, as in Sweden, Norway,

Belgium, Switzerland, Austria, and the Netherlands, ensuring that the national PCC is a key partner of the health authorities in the country.

The scope and role of PCCs changed over the years. In the early days, PCCs were genuinely part of emergency departments and therefore could not be separated from the management of acutely poisoned patients. Later, a new role emerged, namely a phone service, that is to say answering phone calls related to poisonings, which require specific, tailored experience and know-how, together with extensive and dedicated databases on the composition of commercial products and the toxicity of the chemical ingredients they contain. Efforts have indeed been paid to improving the reliability and quality of answers given by PCCs. The American Association of Poison Control Centers established criteria to be met by PCCs [4] and the International Programme for Chemical Safety issued a document on the criteria to be met by PCCs [5].

Databases have always been a major concern for PCCs because the online availability of updated and extensive information on commercially available products, be they pharmaceuticals, pesticides, industrial or household products, or other materials, is essential to ensure a reasonably helpful and reliable phone service. Surprisingly, there are few regulations in both developing and developed countries demanding that manufacturers provide all the information required on the composition of commercial products. Even though confidentiality may be a limitation, there is no reason to believe this cannot be overcome by a collaboration of willing administrations and manufacturers. Information on pharmaceuticals is now widely distributed and the pharmaceutical industry cannot claim this has been actually detrimental. Other types of databases cover the updated knowledge of the scientific community regarding poisonous substances and the management of poisoned patients: in this regard, the Poison Index© and IPCS's INTOX monographs [6] are, or will be, useful tools.

PCCs have focused increasingly on the circulation of information related to poisonings and their management and prevention. Therefore, the term Poison Information Centre tends to be used more commonly than Poison Control Centre. Obviously, in many developed countries, physicians have a better knowledge on the management of acute poisonings, and the public is demanding more and more direct information on poisonings, be they real or suspected. In some instances, these questions are asked via the family physician. Poison Information Centres indeed receive more and more phone calls on a wider variety of issues from food hygiene to water pollution, from drug abuse to occupational exposure, and these queries are becoming less often related to acute poisonings requiring immediate advice for the best way to manage the patients, but require extensive literature survey and an approach similar to that of medical diagnosis.

Although the management of poisoned patients is still a central theme in PCCs and will undoubtedly remains to, another trend is emerging. By and large, more and more physicians have the equipment and training required to treat a wider array of poisoned patients, in particular because specific (e.g. antidotal) therapeutic measures are in practice seldom needed or available.

Clinical toxicology centres [7] will nevertheless still be needed to ensure that the small fraction of severely poisoned patients requiring highly specialized treatments will be given these treatments. At any rate, the current and welcome trend is that more and more poisoned patients are actually treated in general hospitals.

The field of toxic effects related to drug and chemical exposure is evolving from concern essentially based on acute toxicity to chronic adverse effects, including carcinogenicity or immunotoxicity, for instance. Not unexpectedly, environmental medicine, as discussed later in this volume (see Chapter 34), is an expanding field and toxicologists will have a major role to play in this new area. This role is unlikely to be based on the management of poisoned patients (i.e. clinical toxicology), but instead on the ability to combine medicine and toxicology in an integrated approach to intoxicated human beings (i.e. human toxicology). Medical skills for the diagnosis and management of diseased patients will always be essential for human toxicologists, but simultaneously they will have to devote more time to epidemiological studies, post-marketing surveys of chemicals (toxicovigilance), risk analysis and communication, to meet the needs of the next century.

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Human Toxicology, J. Descotes (Ed.)

V. Danel and Ch. Bismuth

1. Management of acute poisonings

Acute poisoning is one of the most frequent emergencies in developed countries, and it is a major cause of death in young people from developing countries. Suicide attempts with pharmaceutical drugs are by far the commonest circumstances of acute poisoning. Accidental poisonings occur less frequently, but as chemicals are often involved, they may be much more severe (Table 1.1). Chronic poisonings, particularly in an occupational setting, require quite a different approach and will not be dealt with in this chapter.

Toxicants	**Relative frequency (%)**	**Mortality (%)**
Pharmaceuticals:	80	1.4
– psychotropic drugs	70	<1
– cardiotropic drugs	4	6
– analgesics	4	1
– others	2	0
Drugs of abuse	5	1
Household products (when ethanol and trichlorethylene excepted; mortality = 0)	9	15
Pesticides (mostly paraquat & weed killers)	3	30
Industrial products (carbon monoxide, cyanide, strong acids)	2	30
Plants (mushrooms) and animals (snakes, insects)	1	<10

Table 1.1. *Incidence and mortality of acute poisonings in European Intensive Care Units*

The management of acutely poisoned patients includes the following steps:
- assessment of vital signs and first emergency measures;
- full patient evaluation (including history, physical examination and laboratory analyses);
- appropriate treatment to reduce absorption and/or enhance elimination;
- use of specific antidotes.

ASSESSMENT OF VITAL SIGNS AND EMERGENCY MEASURES

Even though it seems obvious, it must be stressed that no specific treatment can be effective without prior "aggressive" supportive measures. Similarly, no detailed physical examination should be carried out without recognizing that vital disorders are under correction or have been corrected. Mortality and morbidity in acute poisonings are more closely related to immediate complications and/or the lack of early supportive treatment than to any specific elimination or antidotal therapies. The general predictive factors of mortality in acute poisonings are listed in Table 1.2.

– **Age**
– **Involved substance**: relative safety of pharmaceutical drugs, in contrast to household and industrial products, and to some pesticides.
– **Absence of coma**: mortality is 4 times higher in conscious poisoned patients.
– **Delay** between poisoning and hospital admission: mortality with psychotropic drugs is 2 and 4 times higher when delay is over 12 hours and 24 hours, respectively.
– **Cardiac failure**, **convulsions** or **inhalation pneumonia** prior to hospital admission.
– **Admission in a general ward** prior to admission in an intensive care unit (even in poisonings with delayed symptoms).

Table 1.2. *General predictive factors of mortality in acute poisonings*

It is also emphasized that acute poisonings should be considered as a dynamic state often evolving hours after admission [1]. This is mainly due to the type, mechanism(s) of toxicity and route of entry of the toxic substances involved. In some cases, clinical or biological signs develop several hours after absorption (Table 1.3).

Amanita sp. mushrooms	Paracetamol
Colchicine	Paraquat
Cortinarius sp. mushrooms	Rodenticides anticoagulants
Ethylene-glycol	Trichlorethylene
Methanol	Tricyclic antidepressants
Nitriles (cyanides)	

Table 1.3. *Major poisonings with a delay of several hours between exposure and first clinical and/or biological features*

Failure to appreciate the potential for serious toxicity is a major concern in the management of poisoned patients [2]. Therefore, physical examination must be repeated several times during the first 24 hours. Oxygen therapy and

respiratory assistance, correction of hypotension by fluids and/or sympathomimetic amines, treatment of dysrhythmias and convulsions, are the first measures to consider [3].

Assisted ventilation is clearly a life-saving procedure in a great number of non comatose poisoned patients. This is particularly true with cyanide, chloroquine, β-blocking agents and salicylates, and no other therapy, whether specific or not, can be advocated or even discussed if the need for artificial ventilation is ignored. Severe hypoxemia is indicative of additional pulmonary disease: infection, atelectasis, aspiration pneumonia, hypoventilation or oedema.

Unconsciousness is one of the most frequent features (Table 1.4) because acute poisonings with psychotropic drugs are so common. Coma is characterized by a lack of neurological focal signs. Pupils are symmetric, equal in size and reactive to light. The initial diagnosis should be reconsidered when pupil asymmetry is noted. Even in that case, electroencephalography may help confirm the diagnosis; however, if any doubt remains, CT scan must be performed without delay. In contrast to other causes of coma and provided initial cerebral hypoxia has been avoided, coma in acute poisonings has paradoxically a "good" prognosis value. By contrast, consciousness is not necessarily a sign of good prognosis (Table 1.2). In fact, it must be borne in mind that some highly toxic substances, such as cardiotropic drugs, do not induce coma.

Coma associated with	Major toxic substances
Hypotonia, hypotension	Benzodiazepines Long-acting barbiturates Tricyclic antidepressants Meprobamate Phenothiazines, Ethanol Carbon monoxide
Hypotonia, myosis and slowed respiration	Opiates
Convulsions, salivation, myosis, sweating, wheezing	Organophosphates
Hypertonia, hyperreflexia and mydriasis	Tricyclic antidepressants Anticholinergic agents Strychnine Phencyclidine, Amphetamines
Hypotension, shock, vomiting	Iron, iodine, mercury salts Acids, Alkalis, Corrosives
Convulsions, hypotension and bradycardia	Carbon monoxide, Cyanide β-blocking agents Organophosphates

***Table 1.4**. Clinical features associated with coma and major toxic causes in poisoned patients*

Peripheral **circulatory failure** is often difficult to assess clinically as the typical features of shock may not be seen in the presence of central nervous depression and hypothermia. The treatment of shock in poisoned patients should not be started before airways have been cleared and hypoxemia corrected, since these measures alone often improve the circulation. In addition, in the case of a sustained fall in blood pressure, arterial blood pH, $PaCO_2$ and standard bicarbonate should be determined and corrected if necessary. Cardiac arrhythmias contributing to a diminished cardiac output that fails to respond to these measures should be corrected. If hypotension persists, hemodynamic measures include pulmonary artery catheterization and/or echocardiography. Circulatory failure is not due to one single mechanism and the respective roles of hypovolemia, vasodilatation or myocardial failure must be ascertained.

Hypothermia is defined as a fall in rectal temperature below 36°C. Body temperature must be monitored with a low-reading thermometer, especially when sedative and hypnotic drugs or ethanol are involved. Hypothermia, even when profound, is seldom life-threatening in itself. Core temperatures as low as 20–22°C are compatible with full recovery. Although hypothermia may contribute to shock, acidemia and hypoxia, most symptoms are actually related to the toxic substance involved. Passive rewarming methods are adequate in most cases.

Hyperthermia may be life-threatening, as in cocaine or amphetamine poisonings (see Chapter 17). External cooling must be started without delay. In acute poisonings with monoamine oxidase inhibitors, artificial ventilation and the use of a neuromuscular blocking agent may be life-saving (see Chapter 6). The neuroleptic malignant syndrome may develop in any patient receiving neuroleptic agents on a long-term basis. The main clinical features, which develop over 24 to 72 hours, are hyperthermia, muscle contractions and hypertonia, fluctuating consciousness and autonomic instability. Often compared to malignant hyperthermia, the relationships between both conditions are unclear. Treatment usually combines dantrolene and cooling.

In all cases, the state of hydration, plasma urea and electrolytes, together with the acid-base status, must be carefully monitored. Any disorder should be considered as a possible diagnosis clue and/or as evidence of early complications.

Convulsions may be observed following the ingestion of convulsant drugs, after a severe hypoxic episode, or in relation to the withdrawal of benzodiazepines, alcohol or barbiturates (Table 1.5). The use of flumazenil, a specific benzodiazepine antagonist, must be cautious in poisonings with psychotropic drugs. By suddenly suppressing benzodiazepine effects, it may provoke seizures in patients who simultaneously ingested convulsant drugs, such as tricyclic antidepressants, or in patients with a history of epilepsy [4]. Hypoglycemia must be ruled out by the intravenous injection of hypertonic glucose. Treatment of convulsions with benzodiazepines (diazepam, clonazepam), or short-acting barbiturates (thiopentone) in severe cases, is urgently required. Furthermore, the patient should be intubated to avoid cerebral hypoxia and sequelae. Some convulsant drugs require specific treatment: glucose after

Symptoms	Major toxic substances
Myoclonic jerks	Barbiturate withdrawal Benzodiazepine withdrawal Bismuth salts (chronic) Hypocalcemic drugs Methyl bromide Tricyclic antidepressants
Status epilepticus	Cocaine Ethylene-glycol Isoniazid Metaldehyde, Paraldehyde Strychnine Theophylline (child)
Neuro-muscular hyperexcitability	Chloralose Hypoglycemic agents Lithium Water intoxication

***Table 1.5**. Major poisonings associated with convulsions*

insulin injection, pyridoxine in isoniazid poisoning. Electroencephalography should confirm that the treatment is adequate and has effectively suppressed any ongoing electrical seizure activity.

PATIENT EVALUATION

History and physical examination

Circumstantial evidence often leaves little doubt that a patient has ingested a poisonous substance. This is particularly so in self-poisoned patients who, before they become drowsy or lose consciousness, intimate what they have done. It will also be obvious in patients who take elaborate precautions to avoid premature discovery, but leave a letter. Nevertheless, the history is most often unreliable: the number and exact amount of the toxic substances involved as well as the time elapsed between absorption and admission, are seldom known with certainty. In that respect, the so called lethal doses, which are often considered important when dealing with poisoned patients, are actually of little practical value clinically [5]. Even the route of absorption may be ignored in some cases. In fact, it is important to remember that acute toxicity may occur by routes other than ingestion or inhalation. Some toxic substances, such as weed killers and certain insecticides, may be readily absorbed through the skin

or the eyes. Toxic chemicals produced for industrial use may also be absorbed by these routes, and acute salicylate overdose has occurred following the use of methyl-salicylate ointment on extensive skin lesions [3].

It goes without saying that physical examination must be detailed but apart from assessing vital functions, the examination of poisoned patients has some particularities [6–8]. For example, careful examination of the skin may bring helpful clues regarding diagnosis: needle tracks suggesting addiction, blisters and local oedema suggesting rhabdomyolysis (often associated with barbiturate or ethanol poisonings), a red flushed skin associated with anticholinergic poisonings, slate-grey cyanosis suggesting methemoglobinemia or sulphemoglobinemia... The absence of bowel sounds may result from the ingestion of anticholinergic substances. Hyperpnoea may be indicative of metabolic acidosis (as in alcohol or glycol poisonings) or direct respiratory centre stimulation (salicylates, dinitrophenol), whereas bradypnoea suggests opiate poisonings. Neurosensorial symptoms, such as tinnitus or coloured vision, are very often due to poisonings and must be carefully looked for. The patient's breath may also provide helpful information [9]: in addition to the well-known odour of ethanol, one may smell petroleum distillates, the garlic-like odour of arsenic or organophosphates, the almond-like odour of cyanide, the rotten-egg odour of disulfiram or hydrogen sulphide, or the glue-like odour of toluene. However, diagnosis should not be ruled out when these signs are lacking. In fact, any possible information collected from the patient's family, from early witnesses and from the nursing staff, will help determine the nature of the poisoning and guide laboratory analyses.

A 12-lead electrocardiograph should complete the physical examination. Dysrhythmias or conduction delays may be in evidence, suggesting poisoning by cardiotoxic drugs such as tricyclic antidepressants. Chest radiography will confirm possible pulmonary complications, namely aspiration pneumonia, cardiogenic or non-cardiogenic pulmonary oedema. However, its value as a diagnosis tool is less clear in common practice.

Finally, one must keep in mind that all symptoms should correspond to the presumed cause of poisoning. Any physical sign that does not fit should lead one to consider other toxic causes, an associated disease, such as trauma, or early complications of poisoning.

Laboratory analyses

Biological analyses. In most instances, biological analyses take precedence over toxicological analyses [10]. This is particularly true in acute poisonings as treatment must always aim at correcting existing, life-threatening, metabolic disorders. Furthermore, biological analyses may help in confirming the diagnosis of poisoning and in assessing prognosis. For example, metabolic acidosis, which is hazardous in itself and must be corrected when severe, is an important clue for the diagnosis of glycol or alcohol poisonings (see Chapter 24). An increased anion gap (Table 1.6) as well as an increased osmolar gap further

support the suspicion, which must be confirmed by toxicological analyses. Similarly, hypokalemia is often observed in severe chloroquine or theophylline poisonings whereas hyperkalemia may lead to the early use of digoxin specific antibodies in digitalis poisonings. Table 1.7 summarises the main biological analyses that are required in an emergency situation and expected results. Once diagnosis is confirmed by toxicological analyses, the doctor in charge must make sure that all metabolic disorders are fully explained by the toxic substances involved or by expected complications.

Cyanide	Isoniazid
Ethylene-glycol	Paraldehyde
Iron	Salicylates

Table 1.6. *Major toxic causes of anion gap metabolic acidosis*

Toxicological analyses. The laboratory diagnosis of poisonings is considered extensively elsewhere in this volume (see Chapter 2). Toxicological analyses may be needed to confirm the diagnosis, to assist therapeutic decisions, to assess prognosis and to assess the efficacy of treatment [11,12]:

(1) *Confirming diagnosis.* Laboratory analyses of blood, gastric aspirate or urine are the only way to ascertain the diagnosis of poisonings, provided samples are obtained at the right time, i.e. early in the course of poisonings. It is good practice, when poisoning is suspected but no history is available, to centrifuge blood samples and store plasma at –20°C. In fact, the idea of a blood or plasma bank to allow future analyses is quite common. Similarly, it must be emphasized that urine is a very good diagnosis tool. Therefore, urine samples might also be stored systematically. This practice has proved useful for retrospective diagnosis and avoids extensive and expensive analyses.

The reliability of diagnosis depends on the specificity of the selected analytical methods. Many methods used for emergency screening lack specificity. Highly specific methods are preferred for diagnosis purposes. In any case, the closer is the communication between the referring doctor and the analytical toxicology laboratory, the more reliable are the results.

Qualitative results are adequate in most cases. When quantitative results are provided, the relationship between poison blood levels of the toxic substance and the intensity of symptoms should be determined [13]. This relationship has been established for a few compounds, for example, ethanol, long-acting barbiturates, meprobamate and phenytoin (Table 1.8). In salicylate and theophylline poisonings, a close relationship between the intensity of symptoms and blood levels has been shown. In this respect, it should be borne in mind that toxicokinetic data often differ from pharmacokinetic data. For example, peak blood levels are often delayed when compared to pharmacokinetic data. The association of low blood levels with severe symptoms raises the question of unsuspected associated toxic substances.

Toxic substances	Biological analyses	Expected results
Alcohols	blood glucose (child)	hypoglycemia
	measured and calculated osmolality	osmolar gap
Cyanide	arterial blood gases	metabolic acidosis
	blood lactate	hyperlactatemia
Methanol and ethylene glycol	arterial blood gases	metabolic acidosis
	serum electrolytes	anion gap
	measured and calculated osmolality	osmolar gap
Colchicine	prothrombin time	decrease
	hemogram	leucopenia thrombocytopenia
Salicylates	arterial blood gases	respiratory alkalosis or metabolic acidosis
Digoxin	kalemia	hyperkalemia
Theophylline	kalemia	hypokalemia
Chloroquine	kalemia	hypokalemia
Nitrites, Chlorates and Nitrobenzene	methemoglobinemia	
Organophosphorus	cholinesterase	decreased activity
Raticides	prothrombin time	decrease
Rust removers	calcemia	hypocalcemia

Table 1.7. *Biological analyses required in an emergency situation*

Long-acting barbiturates	Salicylates
Ethanol	Theophylline
Meprobamate	Methemoglobinemia
Phenytoin	

Table 1.8. *Toxic substances with a relatively good relationship between blood levels and clinical status*

(2) *Assisting therapeutic decisions.* As stressed before, toxicological analyses are not required to determine the need for supportive care which is based on clinical findings and biological analyses. Nevertheless, toxicological analyses may help in the making of therapeutic decisions in some instances, as summarised in Table 1.9. However, toxicological analyses are clearly only part of the problem. For example, the indication of hemodialysis in lithium poisoning is based not only on blood levels, but also on the history and, above all, on the clinical status of the patient. Lithium blood levels are nevertheless needed in

Toxic substances	Possible specific treatment
Digoxin	digoxin specific Fab fragments
Ethanol	differential diagnosis, hemodialysis
Ethylene glycol	hemodialysis
	ethanol or 4-methylpyrazole
Iron	deferoxamine
Lithium	saline diuresis, hemodialysis
Methanol	hemodialysis, ethanol
Paracetamol	N-acetylcysteine
Phenobarbitone	alkaline osmotic diuresis
Salicylates	alkaline diuresis, hemodialysis
Theophylline	hemoperfusion

Table 1.9. *Toxicological analyses required in an emergency situation*

order to take the appropriate decision. In digoxin poisonings, digoxin blood levels are not a very reliable prognosis factor as compared to hyperkalemia and cardiac dysrhythmias (see Chapter 10). However, when considering the cost of digoxin-specific antibodies, digoxin blood levels indeed play a role in the decision. In paracetamol poisonings, antidotal treatment is mandatory as soon as the supposedly ingested dose is toxic (see Chapter 12). N-acetylcysteine should be started without delay even though paracetamol blood levels cannot be determined immediately.

In fact, toxicological analyses are not required for the initial prescription of an antidote. However, it may be useful or even mandatory for subsequent administrations of several antidotes, such as ethanol or 4-methylpyrazole in ethylene glycol poisoning, N-acetylcysteine in paracetamol poisoning, chelating agents in heavy metal poisoning or deferoxamine following ingestion of iron salts.

(3) *Assessing prognosis*. In poisonings with lesional toxic substances, such as paracetamol, paraquat or iron salts, toxicological analyses are essential for assessing prognosis, particularly when few symptoms are noted in the early phase [14].

(4) *Assessing the efficacy of treatment*. When the ingested dose is known, the amount of toxic substance removed by either gastric emptying or gut decontamination can only be determined by toxicological analyses. The usefulness of invasive methods, for instance whole bowel irrigation, hemodialysis or hemoperfusion, can also be assessed [3,13]. Serial toxicological analyses of blood, urine or dialysate samples, are required to determine the efficacy of methods enhancing elimination, especially when limited information is available in the literature.

Modalities for the evaluation of treatments preventing absorption or promoting elimination are three-fold. Firstly, the amount of toxic substance actually removed from the body should be determined as clearance values may be

misleading: depending on the volume of distribution, a high clearance rate indeed may well correspond to the elimination of only very small amounts. Secondly, results obtained with the new elimination method under evaluation should be compared to spontaneous elimination by the body and by the best established methods in order to determine whether this new method is more effective. Thirdly, the clinical course and outcome must be taken into account. When the new method is not more effective than established methods, it should be less invasive, cheaper or easier to perform.

APPROPRIATE MEASURES TO REDUCE ABSORPTION

Skin

The skin is the most common route of entry for chemicals used in the industry (alcohols, cyanide, phenols, hydrofluoric and oxalic acids...), in agriculture (insecticides, pesticides...) or at home (household products). Poisonings are usually accidental. Immediate treatment aims at reducing the direct caustic or irritating effects of the substance, and at preventing further absorption (pesticides, phenols). Immediate, copious, and prolonged irrigation of the skin with tap water is, by far, the best way to prevent further absorption. The same procedure is advised for the eyes. No antidotes, except calcium gluconate on hydrofluoric acid skin burns (see Chapter 32), have been shown to neutralise caustic substances.

Gastrointestinal tract

Evacuation of the stomach content can be achieved by provoked vomiting or gastric lavage. Neither method should be attempted in poisonings with petroleum distillates, foaming substances or corrosives. Vomiting should only be provoked in conscious patients. Various drugs including apomorphine and syrup of ipecacuanha have been recommended.

Apomorphine is an opiate derivative which may cause protracted vomiting and central nervous system depression. Its efficacy, in terms of the amount of toxic substance actually removed from the stomach, is so far largely unknown. Unless administered immediately after ingestion in a conscious adult patient, it should be avoided. Side-effects are only partially reversed by naloxone.

Syrup of ipecacuanha may be useful, especially in children, provided its limitations are well understood [15,16]. It should be prescribed and administered under strict medical control, very early in the course of poisoning, namely within one hour after ingestion of a toxic substance. The average onset delay is about 15 minutes and a second dose can be given after 20 to 30 minutes. Adverse toxic effects may be observed. Protracted vomiting lasting more than two hours after the last dose must be ascribed to the ingested toxic substance and not to ipecacuanha. Administration of activated charcoal may be delayed

by previous administration of ipecacuanha. Finally, although effective vomiting may be produced, it is impossible to ascertain whether a significant amount of the poison has been eliminated. Therefore, when the ingested substance is highly toxic, gastric lavage, associated or not with activated charcoal, is more appropriate. Ipecacuanha use must be questioned in mild to moderate adult poisonings in which activated charcoal is said to be effective [17].

Gastric lavage is not advisable outside the hospital. Vomiting and inhalation of gastric contents are frequent complications in inexperienced or careless hands. Gastric lavage should only be carried out in patients with an adequate gag reflex or in patients intubated with a cuffed endotracheal tube. Although gastric lavage is a long and unpleasant procedure, both for the patient and the nursing staff, and though its efficacy has not yet been adequately assessed, it is still recommended and probably too often performed [18–20]. Gastric lavage should never be considered as a punishment for the recidivist or the disobedient child, as no particular dissuasive effect has been documented. Nevertheless, gastric lavage is of great value in poisonings with highly toxic substances, especially when ingestion has occurred a few hours before admission. It is probably valuable even later in poisonings with anticholinergic drugs and perhaps in deeply unconscious and severely ill patients who are already intubated and in whom gastrointestinal motility may be markedly slowed. In this situation, toxicological analyses of gastric samples may be useful in assisting the therapeutic decision. On the other hand, gastric lavage is highly questionable in mild to moderate poisonings, especially with tranquillisers, such as benzodiazepines. In these circumstances, activated charcoal is probably just as efficient as gastric lavage, and far less hazardous.

Whole-bowel irrigation with a polyethylene-glycol electrolyte solution is seldom recommended. It may be used in massive poisonings with highly toxic substances that are not well adsorbed by activated charcoal [21]. It has been recommended in iron poisonings and following the ingestion of cocaine packets or of vials of crack cocaine by drug dealers [22,23].

Cathartics and **laxatives**, such as magnesium sulphate or sorbitol, are probably not essential in acute poisonings but are sometimes associated with other measures [24]. Sorbitol may be associated with activated charcoal when given repeatedly.

Cholestyramine, previously recommended for interrupting the enterohepatic cycle of digitoxin or tricyclic antidepressants, is no longer used, activated charcoal being more effective.

Activated charcoal prevents gastrointestinal absorption and enhances the elimination of many substances [25,26]. Prevention of absorption results from the ability of activated charcoal to adsorb a wide variety of substances onto its surface. In acute poisonings, the most important determinants of activated charcoal efficacy are the time interval before administration and the amount of ingested activated charcoal. Activated charcoal must be given as soon as possible, preferably within 30 minutes after ingestion. However, in acute poisonings, the gastrointestinal absorption of drugs may be considerably

Aspirin	Phenobarbitone and other barbiturates
Carbamazepine	
Dapsone	Phenytoin
Digitoxin	Quinine
Digoxin	Theophylline

***Table 1.10**. Major poisonings in which multiple-dose activated charcoal may be useful (adapted from Ref. [27])*

delayed and thus, activated charcoal may still be effective when administered within 24 hours of drug ingestion. For an increased adsorbing efficiency, high doses of activated charcoal are administered, usually 50–100 g in adults. In children, the recommended dose is 1 g/kg. Ideally, the ratio of charcoal to toxic substance should be 10:1. Activated charcoal does not adsorb alcohols (ethanol, methanol), ethylene glycol, iron salts, cyanide, or lithium [25]. However, ethanol does not prevent the adsorption of associated substances. Enhanced elimination results from the adsorption, in the gastrointestinal lumen, of compounds that:

(1) are actively excreted into the bile (digitoxin, tricyclic antidepressants);

(2) are actively secreted into the intestine (digoxin); and

(3) diffuse passively into the intestine (gastrointestinal dialysance).

When there is an excess of activated charcoal in the gastrointestinal tract, a persistent concentration gradient will develop, resulting in a constant passive diffusion of toxic substances from the systemic circulation to the gut lumen, thereby increasing systemic clearance [27]. It is well established that repeated oral doses of activated charcoal enhance the elimination of numerous toxic substances [27,28] (Table 1.10). Considering the gastrointestinal dialysis effect of multiple doses of activated charcoal, weakly protein-bound substances with a small volume of distribution will be best removed from the body. As with hemodialysis, repeated measurements of the toxic substance blood levels might help assess this particular toxicokinetic effect of activated charcoal. However, the clinical benefit of repeated doses is less clear: a reduced morbidity and mortality have not been shown to be achieved [29]. Adsorption by activated charcoal is non-specific and the administration of drugs or antidotes together with activated charcoal must therefore be avoided.

Activated charcoal must be administered slowly over 10 to 15 minutes to prevent vomiting resulting from a rapid ingestion. In comatose patients, intubation with a cuffed endotracheal tube is required before activated charcoal administration through a naso-gastric tube. Constipation is frequent with repeated doses and is less likely when charcoal is given with a mild cathartic such as sorbitol. Massive inhalation of activated charcoal may result in acute respiratory distress syndrome [25].

Gastrointestinal decontamination is a highly controversial issue [9,30–32] and some clinical studies have even strongly questioned the need for gastric emptying [33,34]. Nevertheless, the main indications of gastrointestinal decontamination can be summarised as follows:

(1) *In conscious patients*: one single dose of activated charcoal is adequate in mild to moderate poisonings. When the presumably ingested dose is very low, no gastrointestinal decontamination is advised. Following the ingestion of highly toxic substances, gastric lavage must be performed but its efficacy highly depends on the lapse of time between ingestion and admission. Following gastric lavage, single or repeated doses of activated charcoal are administered depending on the toxicokinetics of the substance.

(2) *In unconscious patients*: gastric lavage and activated charcoal are often associated, especially when very toxic and/or lesional toxic substances have been ingested. The clinical benefit is doubtful in circumstances when moderately toxic substances, such as tranquillisers, have been ingested. In any case, the potential risks must be weighed against the expected benefits [35].

APPROPRIATE MEASURES TO ENHANCE ELIMINATION

Hepatic elimination

Most toxic substances are metabolised by the liver. The induction of microsomal enzymes by chronic exposure of various chemicals (e.g. phenobarbitone, hydantoins, organochlorine compounds, alcohol) results in increased liver biotransformation, but these findings cannot be used in acute toxicology. Nevertheless, the importance of hepatic metabolism must be stressed. On the other hand, the toxicity of compounds activated by hepatic metabolism (e.g. paracetamol) is increased by microsomal enzymatic induction.

The contribution of metabolism to the removal of toxic substances from the body must be emphasized. Often underestimated, it must be taken into account when assessing other elimination methods, such as hemodialysis or hemoperfusion.

Pulmonary elimination

Volatile substances, such as chlorinated solvents, carbon monoxide and alcohol, are eliminated via the lungs. Measurement of the eliminated amount is possible only in specialised units. In massive poisonings with solvents or alcohol, artificial hyperventilation may be proposed to enhance pulmonary elimination. When alcohols or solvents are involved, toxic gases must be evacuated from the medical ward to protect the medical and nursing staff.

Renal elimination

When considering the few substances significantly eliminated unchanged by the kidneys, two methods for increasing renal elimination are available. Raising the urinary pH enhances the renal elimination of weak acids, such as slow-acting barbiturates or salicylates, as the ionised form is not reabsorbed through the tubule ("ion trapping"). Lowering the urinary pH, although theo-

retically valuable in poisonings with weak bases (e.g. tricyclic antidepressants, quinine, quinidine, nicotine and chloroquine) has no practical value since the biotransformation of these drugs takes place mainly in the liver [36,37].

Neutral osmotic diuresis (infusion of a hypertonic solution of mannitol and 10% dextrose) is no longer used in the majority of the poisonings (e.g. phenothiazines, meprobamate and benzodiazepines) for which it was formerly proposed. All these drugs are predominantly metabolised in the liver and/or excreted by the kidneys as inactive metabolites.

Alkaline osmotic diuresis (forced diuresis) which associates bicarbonate, mannitol and 10% dextrose given intravenously, is indicated in poisonings with slow-acting barbiturates or salicylates. It should be started only when toxicological analyses have confirmed that blood levels are high enough to potentially result in severe poisoning. Furthermore, forced diuresis is a metabolically invasive procedure requiring close supervision, preferably in an intensive care unit [38]. The main indications of forced diuresis are listed in Table 1.11.

Toxic substances	Method	Comments
Salicylates	alkaline diuresis hemodialysis	Rehydration, respiratory assistance and supportive care usually adequate
Phenobarbitone	alkaline osmotic diuresis hemodialysis	Respiratory assistance and general supportive care usually adequate
Methanol	hemodialysis	Antidotal treatment (ethanol) must be associated
Ethylene-glycol	hemodialysis	Antidotal treatment (ethanol or 4 MP*) must be associated
Lithium	saline diuresis	General supportive care often adequate
	hemodialysis	When indicated, to be repeated
Theophylline	hemoperfusion	Correction of hypokalemia and propranolol may be adequate

(*4 MP = 4-methylpyrazole)

Table 1.11. *Major poisonings justifying renal or extra-renal elimination*

Although it can dramatically increase phenobarbitone renal clearance, it is unclear whether recovery occurs significantly quicker. Therefore, forced diuresis must not be considered as an essential therapy, as compared to artificial ventilation, gastrointestinal decontamination and nursing care. In severe aspirin poisonings, alkaline osmotic diuresis or alkaline diuresis [39] is not as important as intensive rehydration and artificial ventilation. Complications due to forced diuresis include pulmonary oedema, cardiac arrhythmias or cardiac failure [36].

Saline diuresis (infusion of 1–2 l saline/day) increases the renal elimination of bromide and lithium, provided dehydration has been corrected. However, in severe symptomatic lithium poisonings, hemodialysis is more effective.

Exchange transfusion

The best indication of exchange transfusion, and probably the only one in clinical toxicology, is severe methemoglobinemia, especially when associated with hemolysis as in chlorate poisonings (see Chapter 20). In these circumstances, the specific antidote methylene blue is often ineffective and exchange transfusion must be started without delay. Similarly, exchange transfusion is used to treat severe sulphemoglobinemia as no specific therapy is available.

Hemodialysis

Although it has been recommended for a wide variety of toxic substances, only relatively few severely poisoned patients actually benefit from hemodialysis. To be effective from a toxicological point of view, hemodialysis should enhance elimination of the toxic substance by 30% at least as compared to spontaneous body clearance. The substance physical characteristics are the major limiting factors of hemodialysis efficacy [40,41] (Table 1.12). Furthermore, plasma levels should ideally correlate with clinical symptoms so that toxicological analyses can confirm the role of hemodialysis in the duration of poisoning.

Factors	Comments
Volume of distribution (Vd)	Poisons with a high Vd (>1 l/kg) cannot be effectively removed from the body
Molecular charge	Water-soluble or ionised substances are more effectively removed
Protein binding	Highly bound substances are poorly removed
Molecular weight	Substances with a high molecular weight (>300 d) are poorly removed

Table 1.12. *Toxicokinetic factors in hemodialysis (adapted from Ref. [40])*

The efficacy of hemodialysis cannot be assessed clinically: the vast majority of acutely poisoned patients recover with supportive treatment alone. Moreover, the role of prolonged intestinal absorption, hepatic metabolism and urinary excretion must be taken into account. When available, kinetic data are compared to known toxicokinetic, instead of pharmacokinetic, data on the toxic substance involved [42]. As mentioned earlier, a high clearance rate is not adequate for drawing conclusions about hemodialysis. When the volume of distribution is large enough, the amount of the substance actually removed

may be negligible as compared to hepatic elimination. Hemodialysis is probably most useful in poisonings with substances largely metabolised to toxic metabolites, such as methanol or ethylene glycol (see Chapter 24). In ethylene glycol poisoning, the correction of metabolic acidosis and renal failure, and an enhanced elimination of ethylene glycol from the body are obtained with hemodialysis. Hemodialysis is always associated with ethanol or 4-methylpyrazole therapy. Methanol is poorly eliminated by the kidneys and therefore hemodialysis is mandatory in most methanol poisonings, as it is the only means of efficiently eliminating the toxic compound. Provided supportive care is properly carried out and whatever the blood levels, hemodialysis is seldom useful in salicylate or phenobarbitone poisonings. On the other hand, dramatic results have been observed in severe symptomatic lithium poisonings. Clearly, hemodialysis does not preclude gastrointestinal decontamination, antidotal therapy and supportive care. Even though hemodialysis is carried out, supportive care remains an essential part of the treatment and must be continued until the patient shows signs of full recovery.

In our experience, the complications of poisonings, such as hypotension, convulsions, circulatory failure or adult respiratory distress syndrome, should never be considered as indications of hemodialysis.

Hemoperfusion

Hemoperfusion was introduced in 1965 as a method for removing toxic substances from the body. Although it shows some of the toxicokinetic and patient-related limitations of hemodialysis, hemoperfusion is not limited by high molecular weight, protein binding or poor water solubility [40,41]. Charcoal and resin are the two distinct cartridge types with different drug affinities. Charcoal-coated adsorbent removes both polar (e.g. salicylates and methotrexate) and non-polar drugs as well as their metabolites. Amberlite XAD-4 resin clears non-polar, lipid-soluble drugs (e.g. ethchlorvynol, glutethimide, meprobamate and methaqualone) more effectively than charcoal-coated cartridges. In spite of its theoretical interest, the practical use of hemoperfusion is controversial [43]. There are two situations in which hemoperfusion might be valuable:

(1) *In massive poisonings with sedative drugs* (barbiturates, meprobamate, bromides, lithium), morbidity and mortality are very low with supportive treatment alone. However, these drugs have a high extracellular distribution. As expected, the effectiveness of hemoperfusion is relatively good: between 7% and 20% of the ingested dose can be recovered. Whether these results can be judged satisfactory, life-saving, or insignificant is largely a matter of opinion [42].

(2) *Massive poisonings with lesional toxic substances* (paraquat, amanita phalloides, paracetamol) *or cardiotropic drugs with high mortality* (tricyclic compounds, antiarrhythmic drugs) are another theoretical indication. The use of hemoperfusion in these poisonings is extremely attractive in view of the remarkably high clearance. Unfortunately, the extracellular distribution of these substances is weak and the total excreted amount low.

Use of specific antidotes

Few specific antidotes are available [44]. Only a few may be considered as life-saving in an emergency situation (Table 1.13). In paracetamol poisonings for example, and although there may be no symptoms at all in the early phase, N-acetylcysteine must be administered as soon as possible to be effective (see Chapter 12).

Mechanism	Toxic substances	Specific therapy
Chelating agents	Aluminium	deferoxamine
	Arsenic	dimercaprol (BAL) DMSA, penicillamine
	Copper	penicillamine, DMSA
	Cyanide	dicobalt edetate hydroxocobalamin*
	Iron	deferoxamine*
	Lead	dimercaprol (BAL) calcium disodium edetate (EDTA), DMSA, penicillamine
	Mercury	dimercaprol (BAL) DMSA
	Thallium	potassium ferricyano-ferrate (Prussian blue)
Receptor competition	Benzodiazepines	flumazenil*
	Digitalis	antidigoxin Fab fragments*
	Methemoglobinemia	methylene blue*
	Opiates	naloxone*
	Organophosphates	oximes + atropine
Target competition	Anticoagulants	vitamin K
	Beta-blockers	glucagon* sympathomimetic amines*
	Carbon monoxide	oxygen*
	Cyanide	oxygen*
	Paracetamol	N-acetylcysteine*
Metabolic competition	Ethylene-glycol and methanol	ethanol* 4-methylpyrazole*
Supplement in physiological pathways	Cyanide	sodium thiosulfate hydroxocobalamin*

BAL: British Anti-Lewisite; DMSA: dimercaptosuccinic acid (oral route)
*May be required immediately

Table 1.13. *Antidotes in the treatment of poisonings*

Even when they are available, antidotes may themselves cause serious toxic effects. For example, dicobalt edetate can lead to severe hypotension in mild to moderate cyanide poisoning (see Chapter 26). Physostigmine, sometimes advocated in tricyclic antidepressant poisonings, can cause convulsions, bronchospasm and bradycardia and should now be considered hazardous and obsolete. Analeptic drugs other than true pharmacological antidotes should never be given as a treatment for sedative and hypnotic drug poisonings. The therapeutic half-life of some antidotes, such as naloxone and flumazenil, is much shorter than that of the drugs involved (opiates and benzodiazepines, respectively) and the initial improvement induced by these antidotes may be followed by a disastrous deterioration unless the patient is closely monitored. In fact, it should be borne in mind that true antagonists, such as naloxone or flumazenil, while effectively suppressing the symptoms of poisonings, do not alter the toxicokinetics of the drugs they antagonize. With rare exceptions, patients who are given antidotes should be closely monitored in an intensive care unit.

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2. Laboratory diagnosis of poisonings

INTRODUCTION

The role the toxicology laboratory has to play in the diagnosis, management and follow-up of acute poisonings, is currently a highly controversial issue. A long, but not exhaustive, list of publications has dealt with this topic [1–22,1929,2030,2212]. The term "toxicological screening" is especially misleading as it means different things to different persons. Therefore, when a toxicology programme is to be set up, there is a need for clarification between clinicians and analysts. Many problems have arisen from misunderstandings between the both groups, presumably because of a lack of real partnership.

The limitations of analytical toxicology

These misunderstandings referred to above may arise from a whole host of factors: a lack of a concise definition (and consensus) of what a toxicologist is; a lack of initiative from the analyst (e.g. chemist or pharmacist) on duty; a lack of adequate laboratory equipment; unhealthy competition between clinical chemists and analytical toxicologists and other professionals; a lack of medical knowledge in the case of many analysts; a lack of analytical knowledge for many physicians; a lack of knowledge in basic and advanced pharmaco- or toxicokinetics and a shortage of time for the detection of drugs in biological fluids for many of both professions; a lack of laboratory staff, instrumentation and space (as well other economic or financial aspects) to ensure a 24 hour-a-day service; a lack of updating toxicological screening procedures, as the drug and poison market is continuously changing; a lack of knowledge about the actual performance of analytical methods (which is by far the commonest misunderstanding); a lack of adequate patient and physician identifications; a lack of adequate body fluids sampling, essentially due to workload stress in intensive care units; a lack of appropriate specimens (for example, detecting methemoglobinemia in serum is absolutely impossible even for the best analysts).

It is quite clear that a "negative screen" means very little except that in well-defined conditions, a limited number of substances have not been found in the samples examined. Unfortunately, neither the clinician nor even the analyst

are aware of this on many occasions, as very few people are fully aware of the technical limitations of analytical methods. Checking the performance of analytical methods is very time-consuming and is practically never completed. The best approach is to use quantitative methods because, even though quantitative results may not be important for the medical management of a given patient, this is nevertheless very useful for quality assurance in analytical toxicology.

Quality assurance is absolutely necessary but it results in a tremendous workload for the laboratory (in addition to routine toxicology analysis) and is also very challenging if the analytical toxicologist wants to survive. Most people who are not chemists, do not appreciate the very considerable technical difficulties in measuring ppb (μg/l) or ppt (ng/l) levels of any chemical in any medium. Even for the ppm (mg/l) range, this is far from easy. Analysis of such extremely small quantities requires elaborate and expensive analytical equipment that cannot be available in many laboratories.

The analytical toxicologist and the clinical chemist

The competition between analytical toxicologists and classical clinical chemists is quite considerable and not necessarily bad, if the latter are also using techniques other than immunoassays, which have many pitfalls, especially in the interpretation of analytical results, so that they should be used only very carefully. The analytical toxicologist and the clinical chemist are both partners of the clinician [2030]. They are complementary and should work together within the framework of their recognized competence. Therefore, the analytical toxicologist should not be left with a few of those remaining drops of blood and/or urine after the clinical chemist failed to find any drug or poison. Sampling for the toxicology laboratory should be done immediately and separately (namely for the use of nobody else). The samples will be forwarded to the toxicology laboratory only if necessary, because of the high cost of such investigations.

The analytical toxicologist and the clinician

Many of the prejudices of clinicians towards the toxicology laboratory should be overcome; for example, the presumed unduly late response of the toxicology laboratory which may be due to a number of reasons, not all from the laboratory side, even though the problems are technically unavoidable. It is a fact that many clinicians believe that analytical toxicology serves no purpose and is not necessary for the patient's care. The clinician must clearly treat the patient and not the poison, but in some cases the right diagnosis is only obtained thanks to the toxicology laboratory which does not have an easy task when only minimal information on the medical status of the patient is available. A properly informed analyst helps to keep costs much lower and equally importantly, better results are to be expected [1929].

The role of analytical toxicology

Proper documentation on a poisoned patient is incomplete without analytical toxicology. Analytical toxicology for the clinician should thus be considered as equivalent to radiological imaging for the surgeon. Analytical toxicology is necessary for forensic reasons; any intoxication may have a criminal cause. A further point is that many patients (or their relatives and their insurance companies) will not accept a prolonged hospital stay unless laboratory evidence is available. What use would be a methadone treatment programme without testing for drugs of abuse in the urine? In addition, routine work is needed, otherwise the toxicology laboratory is unable to perform correct and complex analyses in situations when results are of paramount importance. In cases of mixed drug poisonings, such as in the case of polydrug addicts, toxic effects may mask other toxic effects and also drugs of abuse have varied kinetic profiles.

Analytical toxicology is needed not only in the diagnosis of poisonings, but also in the follow-up of patients in cases of aggressive therapy and for pharmaco- and toxicokinetic studies. Even though a patient initially responds to a specific antidote, for example naloxone in heroin overdose, further testing should be considered because of possible multiple poisoning.

The techniques

As quantitative methods for every drug or poisonous substance cannot be available in all laboratories, even though they may be specialized, a regional (or even better international) collaboration between toxicology laboratories is essential. It must also be emphasized that blood (serum or plasma) and urine are not the only biological fluids to be analyzed. Gastric juice (aspirate or concentrated lavage fluid), drugs, unknown powders, plants, can be handled by many laboratories and may quickly lead to a correct diagnosis.

As analytical instrumentation has improved and is still improving, there is no excuse for not using very performant techniques such as bench-top gas chromatography coupled to mass spectrometry (GC-MS). The cost of these instruments has been considerably lowered recently and many have become very user-friendly. It must be kept in mind though, that one single technique has limitations and may not be the only acceptable technique. A reasonable combination of different analytical techniques is the right approach in the 90s, as described below. Many analytical techniques, of which some are briefly defined in the glossary, are now available, namely immunoassays (IAs), gas chromatography (GC), high-performance liquid chromatography (HPLC), and thin-layer chromatography (TLC). Extraction techniques, like liquid–liquid extraction and solid phase extraction (SPE), have been used for over 15 years and have improved during the past decade. New techniques have found applications in toxicology, such as extraction techniques like supercritical fluid extraction (SFE or SCF), and detection or quantification techniques like capillary electrophoresis (CE), ion-chromatography (IC), atmospheric pressure ionization

electrospray-LC-MS and inductive-coupling plasma mass spectrometry (ICP-MS). The current trend is to go more and more to direct sample analysis (DSA) using commercially available devices and instrumentation, enabling on-line sample extraction by column switching [1960], followed by multichannel column analysis, and chemometrically enhanced drug and metabolite identification.

As trends in drug use and the chemicals used for different purposes are changing, the "toxicology screening" must adapt or expand to take into account regional particularities. Chemicals that are no longer commercially available may still be stored in many homes and may be used for suicide attempts or cause accidental poisonings. The long professional experience of both the clinician and the analyst is therefore very useful. We should note in passing that basic education and further training in toxicology should be encouraged in universities. In many medical education curricula all over the world, neither clinical nor analytical toxicology are included or, at most, are very poorly represented.

Sampling of body fluids for analytical toxicology prior to any drug treatment is essential, and performing a second sampling should be encouraged after 1–4 hours (depending on the elimination half-life of the causative substance) to check whether biological fluid levels are increasing or decreasing. Any previously known drug therapy should be notified to the analyst to avoid waste of time in trying to identify and quantify irrelevant drugs.

In the past, clinicians have claimed that most toxicology laboratories did not reliably identify drugs or poisons. Unfortunately, this is often still true. Some of the reasons for this have been mentioned above and efforts are being made to improve the quality of analyses. In particular, the concept of quality assurance, including the sampling, shipping and interpretation steps, is being extensively developed, reviewed and improved. As the clinician's expectations often exceed what the toxicology laboratory can actually do, mutual consultation is one of the major "take-home messages" to retain from this introduction. But first and foremost, in the management of poisoned patients, every possible effort should be made to save their life and to ensure they will be given the best possible care. This was stated as early as 1972 by Roy Goulding as "maintaining the alignment between the ward and the bench" [2].

This chapter will not attempt to survey the excellent standard reference books in analytical toxicology [23–33,1862,1863,2030,2212,2218] nor will it comment on standard pharmacology, clinical toxicology [3–15,2213] and pharmacokinetics publications [34–45,2214,2218] in which plenty of useful information on drugs and poisons can be found. The International Programme on Chemical Safety (IPCS) will soon make available the database "INTOX" with information on the analytical toxicology of a number of toxic substances [1859]. A good summary of what is going on in toxicology (and not merely analytical toxicology) is published every year as the "Year Book of Toxicology" by Irving Sunshine [1735].

THE ANALYTICAL APPROACH

To avoid difficulties in elucidating the cause of a given poisoning, a very comprehensive screening can be performed if time and money are available. This will of course not always be possible and the analytical work will therefore be limited to suspected drugs or poisons only, even though the correct answers may not necessarily appear. Past experience has shown that the information on request forms is not generally reliable or at least incomplete as illustrated below in Table 2.1.

	1979/80 (%)	**1982** (%)	**1991** (%)
Presumption confirmed	26	33	16
Presumption not confirmed	28	32	44.2
No clinical information available	46	35	9.8
Forms filled	56.1	56.5	97
Total number of cases studied	144	359	500

Table 2.1. *Comparison of analytical results with request forms*

Other authors have had similar results [21,46,47]. As can be seen, the filling of request form improved over the past 10 years. In our 1991 study, blood and urine were available in 46.2% of cases only, whereas blood, urine and gastric content were shipped to our laboratory[1] in 30% of cases.

Sampling of biological fluids for toxicological analysis

The proper selection, collection and submission of biological and other specimens for toxicological analysis are of paramount importance, if analytical results are to be accurate and their subsequent interpretation useful in the judgement of forensic and other toxicological cases. All specimens must be collected in clean, dry containers. The amounts indicated below are minimum amounts:

- blood: 10 ml in plain tube and/or on sodium heparin;
- urine: 50 ml;
- gastric juice (aspirate, vomitus): 50 ml.

The laboratory technicians have great difficulties if only insufficient amounts of specimens are available. Unfortunately this happens nearly every day. All specimens should be correctly identified by the patient's name, with the date and time of collection, written in a readable manner. Many toxicology

1 A national (Luxemburg) laboratory independent of the hospitals.

laboratories provide toxicology request forms which should be filled out as carefully as possible. The more useful clinical information is available to the analyst, the greater will be the chance that the laboratory comes up with the right diagnosis in a reasonable time.

Special attention should be brought to collection of urine in drug addicts, for example to avoid all adulteration attempts or substitution [48–52,2032,2033, 2035]. DNA analysis may sometimes be useful [177]. A non-invasive sampling has been studied by Glifield et al. [53]. In addition to the 3 classical specimens, many other substrates are nowadays investigated, like saliva [54,55] hair and nails[1], sweat [56–59,1844,2042] feces [60]. Even skin surface sampling is possible with the use of ion mobility spectrometry (IMS) [61,1952]. A similar method is used in airports by security officers to detect drugs of abuse and explosives in suitcases. Laboratory results of classical clinical chemistry and hematology can be very useful for the diagnosis of intoxications, as summarized in Table 2.2.

– leucocytosis	– hypokalemia
– leucopenia	– hyperkalemia
– hemolysis	– hyponatremia
– prolonged prothrombine time	– hypocalcemia
– osmolal abnormalities	– cholinesterases
– hypoxia and respiratory acidosis	– hypercalcemia
– metabolic alkalosis	– hyperglycemia
– metabolic acidosis and anion-gap	– hypoglycemia
– oxalates in urine	

Table 2.2. *Clinical biochemistry and hematology changes useful for the diagnosis of intoxication*

A selection of tests (see Table 2.3) for the most relevant drugs or poisons which may be requested in emergency situations and for which there are implications in treatment, should be available in all toxicology laboratories.

antidepressant drugs	paraquat
barbiturates	ethanol
carbon monoxide	methanol
paracetamol	isopropanol
cyanide	ethanediol (ethylene glycol)
salicylates	methemoglobin
theophylline	digoxin
lithium	phenytoin

Table 2.3. *Most relevant drug and poison assays*

1 For chronic poisoning only.

As there are as many screening methods as laboratories in the world, one approach which has been in operation for some time has been selected, hopefully to correspond to the state-of-the art" and this approach has so far proved to be useful in our hands. This does not mean that other approaches cannot be used or may not even be better. But in all cases, screening should include as many relevant substances as possible and when only one substance (or its metabolite) is of interest, then a specific method can be used (see references quoted after individual substances). Methods dedicated to the analysis of individual substances or groups of substances will be briefly discussed later in this chapter.

A clear distinction should be made between testing for the diagnosis of acute poisonings and for the identification of drugs of abuse. The US NIDA-5 Approach for the testing of drugs of abuse is not always considered as the best possible approach in other parts of the world. The basic principle of forensic toxicology that independent duplicate analytical assay is compulsory, may also be very useful in clinical toxicology as inadequate or inappropriate treatment due to false diagnosis or the lack of sample double cross-checking, may have dramatic consequences.

Outline of an analytical approach for diagnosis of acute poisonings

Serum or plasma. Alcohol (ethanol) and other solvents are best screened by head-space gas chromatography [62–64]. As a second method, an immunoassay or classical dehydrogenase method is advisable for ethanol. Lithium is detected and quantified by flame-emission photometry [65] or ion specific electrode potentiometry. Screening for acid, neutral and basic substances is performed by GC-MS using 2 different extraction steps at 2 different pH values. The quantification of many drugs can be achieved by HPLC [66]. A battery of immunoassays including those for barbiturates, benzodiazepines, paracetamol, digoxin, digitoxin, tricyclic antidepressants, theophylline, quinidine and anticonvulsants, like carbamazepine, valproic acid, phenytoin and phenobarbital, is performed whenever a sufficient amount of substrate is available. Great difficulties are encountered with group tests like barbiturates and benzodiazepines.

As quantitative results should be obtained for analytical reasons (especially interpretation), if not, for toxicological reasons, therapeutic and toxic range concentrations have been included in the tables. Indeed, an analyst wishing to develop an analytical method needs first to know the concentration range he will have to work with, even though these concentrations may not have clinical consequences. It must also be borne in mind that many concentrations have not been observed under the same analytical conditions and these data should be used cautiously. Many "toxic" concentrations are measured as post-mortem levels and do not reflect a minimum toxic concentration.

On request, carbon monoxide and methemoglobinemia can be performed using a multi-wavelength photometric method with the "CO-oximeter" [67]. Cyanides are detected and quantified by a colorimetric method using chloramine T and a pyridine–barbituric acid solution after diffusion in a Conway cell [28]. Ethylene glycol can be quantified after derivatization with phenylboronic

acid using a gas-chromatographic method [68]. Trichlorethanol and trichloracetic acid after methylation with diazomethane can be quantified by headspace gas-chromatography [69].

Urine. Amphetamines, barbiturates, benzodiazepines, cocaine and opiates are screened using immunoassays. Salicylates, paracetamol, and some organochlorine derivatives are detected by colour reactions ("spot tests"). X-ray fluorescence spectrometry detects organobromine compounds, such as carbromal, but at the same time, it also detects inorganic compounds in the mg/l range. Thin-layer chromatography (TLC) is used to detect acid, neutral and basic substances after extraction at different pH and after acid or enzymatic hydrolysis. Many (but not all) benzodiazepines or their metabolites are not only released from glucuronide conjugates by acid hydrolysis, but are also transformed to aminobenzophenones which are easily detectable by diazo-coupling reactions. This transformation cannot be achieved by enzymatic hydrolysis. GC-MS investigation is indicated in order to clarify the diagnosis when necessary. As many polar metabolites (or even polar parent compounds) are commonly found, it is advisable to derivatize by prior acetylation, silylation or alcoylation to obtain better detectability and quantification [70].

Gastric content. Basically the same analytical techniques are used as in urine (except immunoassays). Heavy metals and some inorganic salts can be detected by X-ray fluorescence spectrometry.

Testing for drugs of abuse. Testing procedures are usually limited to urines. The philosophy of the US-NIDA (now HHS) initial screening includes 5 drugs or groups of drugs only, the opiates, amphetamines, tetrahydrocannabinoic acid (THC-COOH), phencyclidine (PCP) and cocaine metabolites, followed by a GC-MS confirmation step. This philosophy may not be in line with requirements from different countries, and the "all immunoassay approach" including these drugs only, may not be satisfactory. At the least, other frequently abused drugs like ethanol, methadone, d-propoxyphene, buprenorphine, dextromoramide, pentazocine, dihydrocodeine, benzodiazepines, barbiturates and others, should be included. As drug addicts are aware of the limited possibilities of most laboratories, they frequently change their consumption habits, for example by abuse of antitussives instead of heroin [1845].

In many occasions, a nearly complete screening may be necessary as with acute poisonings, but methods with better (i.e. lower) detection limits are required to identify all involved drugs or to exclude low-dose abuse. Quantitative assay for creatinine in all urine specimens may be useful in order to detect unacceptable dilution [71,810,1911,2043,2215]. In some circumstances, such as the regular testing of urine specimens from the same patients of a methadone maintenance programme, confirmation by GC-MS may not be necessary and is a waste of time and money.

For forensic purposes, quantification of some drugs in the blood may be required, especially if human performance testing is desired. So far no consensus on limit concentrations in the blood has been reached among experts except for very few drugs [72–76].

"General unknown" approach

The best approach to analytical toxicology is of course the attempt to identify and quantify all exogenous substances which could explain the symptoms of a presumedly poisoned patient. Excluding some poisons may also be very important.

To implement this, international efforts have been devoted to proposals for a suitable methodology covering as many drugs and poisons as possible. Several methods are discussed in the section on chromatography. If this methodology cannot be used for whatever reasons, it is advisable to look for specific substances in a particular substrate, bearing in mind that substances that are not looked for, are usually not discovered.

Methods for specific drugs

This review will cover as widely as possible the most recent publications so that a suspected drug or poison can be identified or/and quantified. Due to the very large number of substances, no laboratory in the world can have all these methods in a stand-by mode for immediate use. Not all references could be included in this review for the same reason. In any case, imagination is required to adapt one method to the problem encountered in a particular situation in the laboratory. Because there are so many substances, and it was wished to offer useful and rapidly assimilable information, most analytical methods or/and pharmacokinetic data for drugs or poisons will be presented in tables (in alphabetical order within their class). Other recent analytical methods will be briefly reviewed.

GENERAL COMMENTS ON ANALYTICAL METHODS

Immunoassays [2035]

In the past twenty years or so, different types of immunoassays (IAs) have been introduced into clinical chemistry and analytical toxicology [77–80,2050, 2051,2056]. The classical tests are: hemagglutination (HI), radioimmunoassay (RIA), enzyme-multiplied immunoassay technique (EMIT), and fluorescence polarization immunoassay (FPIA).

Criteria to be considered when using Immunoassays

Costs. As IAs are expensive, they should be used only when a large number of analyses of the same type (or single tests) have to be performed or when no other method is available.

Limits of detection (LOD) should cover therapeutic doses. For the testing of drugs of abuse, some laboratories prefer to use cut-off values.

Confirmation. Results obtained with IAs must be given along with a warning that confirmation by a second method is compulsory, except in special

circumstances, for instance a methadone programme. The confirmation should ensure total identification of the involved substances.

Immunoassays vs chromatographic techniques. IAs should be used when a low prevalence (10–15%) of positive results is expected and when the concentration of the substance is relatively low. Chromatography should be preferred when the substance involved is unknown, or when a high prevalence, as in the emergency room, or a "high" concentration of the substance is expected.

Specificity. Expected false negatives should be less than 1% and false positives less than 5%. The major concern with IAs is their lack of specificity. Indeed, many false positives due to interferences may be experienced. It must also be remembered that cross-reactivities are not identical for all substances within the same chemical family. The results normally include the concentration of the parent substance together with many, if not all, metabolites. This is a major difference from chromatographic methods which should be borne in mind when interpreting the results. Many false negatives are due to adulterants, like detergents, acids, salts, alkalis or disinfectants [49–52,1908], to filtration [1720] or the lack of appropriate detection limits [81,2190]. The detection limit is not the same for all substances of one chemical family. Several tests are not usable due to excessively high absorbance in EMIT testing [82]. Interferences due to fluorescence compounds from other drugs, food additives, or residues in relation to medical investigation techniques, may occur in FPIA-tests.

Inappropriate use [83]. All screening methods are presumptive. IAs are genuinely not more than semi-quantitative. For example, in the amphetamine test, a result of 127 ng/ml is extrapolated from a non-linear curve if the highest calibrator used is 100 ng/ml. The assigned value of 127 ng/ml is therefore a gross underestimate because it is measured at saturation of the assay. The only acceptable results are "positive" or not detected, with indications of the method used, for example RIA, EMIT, FPIA, and the "cut-off levels" or LODs. Consequently no quantitative results can be expected without prior analytical separation. IAs are primarily designed for qualitative detection whatever the technique for assaying the drug-antibody interaction.

The use of the "cut-off" concept may create difficulties. For example, the "cut-off" or threshold value for amphetamines is 1 mg/l. An IA result of 0.4 mg/l can only be considered as negative, if the substance compound is identified. If the substance is phentermine with ±30% cross-reactivity, the concentration is actually 1.2 mg/l which should be considered positive. For a correct use of "cut-off" values, it is important to know the exact nature of the substances involved, which is not technically possible at the time.

Additional immunoassay techniques have been recently introduced like Ontrak® [1877], ascend multi-immunoassay AMIA-Triage® [85,613,1805,1806, 1827,1909,2048), Vitalab-Eclair® [1770], Abuscreen® [1901,2199], KIMS-online [2036], cloned enzyme donor assay CEDIA [2044], Frontline [2045,2046], Accupinch [2047], Abusign, MicroLINE Screen-Elisa, Autolyte-Drug Screen, Visualine II monotests [2049], and EZ-Screen® [1924]; these are mostly for those laboratories with a small number of specimens to assay. Others are under

development, like the highly sensitive chemiluminescent techniques [86] and the time-resolved fluorimetric IAs [87].

Chromatographic methods

Recent reviews have been published on these methods [88–91].

Thin-layer chromatography (TLC). This old technique is still very useful for presumptive identification [92–94,2052]. It is easy to handle and inexpensive, but requires skill even with commercial kits. Quantitative work and confirmation are also possible [29,91,95]. However, detection limits may be inadequate in some instances, resulting in false negative results [81]. A review of corrected Rf-values for a better comparison has recently been published [96].

Gas chromatography (GC). This is also an old technique [23,116]. A review of retention indices has been published recently [117] and new developments have been summarized [118]. The main disadvantage is that the substances have to be precisely known in order to select a correct derivatization technique. Another disadvantage is the lack of specificity. Therefore a mass spectrometer as detector is essential. The bench-top mass analyzers including computer software with a good spectra library designed for toxicological analysis, are user-friendly.

Gas chromatography coupled to mass spectrometry (GC-MS). GC-MS techniques have notably achieved great progress since the end of the 50s and an enormous number of papers have been published [70,119–123]. GC-MS procedures used for the toxicological analyses of many substances have been reviewed [124]. However, it must be emphasized that analysts should not only rely on computerized spectral libraries, but should also make any efforts to interpret unknown spectra [119,120]. The major problem with GC-MS is the need for a suitable derivatization, which means that the nature of the substance(s) to detect must be known. Attempts have been made to overcome this problem by using mixtures of derivatizing agents intended to be reactive with various chemical functions. Another limitation to routine GC-MS screening techniques is that unless special chemical treatment is performed, many organic substances, for example ethanol, insulin, paraquat, digoxin, trichloroacetic acid, will not be detected in the same run.

Classic GC-MS with EI-detection has been extended to other techniques such as chemical ionization (CI) techniques. Other techniques, for instance Fast Atom Bombardment (FAB), Laser techniques and MS-MS or tandem-MS, if sub-ng/ml limits of detection are required, have emerged [125-127]. Many of these techniques are not yet used routinely. High-performance liquid chromatography coupled to mass spectrometry (LC-MS), another technique not used routinely, has been developed and will certainly play an increasingly important role as previous derivatization is not always required [115].

High-performance liquid chromatography (HPLC). This technique was developed more recently and it is the most important technique in analytical toxicology. Basic technology and new developments have been discussed

[97,98]. HPLC can be used for screening, especially if coupled with diode array UV-detection [99–111,1785,1834,1960], mass-spectrometry [113] or "on line" photochemical reaction [114]. When totally automated "black box" systems are used [106], the interpretation of results should be very cautious. Atmospheric pressure chemical ionization and electrospray technique are now becoming routine and will be developed further [115]. Ghosh [110] presented a collection of 650 drugs which can be measured using HPLC. Reviews of standardized systematic screening by HPLC using a retention index library were published [1947,1958].

The most promising techniques in analytical toxicology at the time of writing are capillary electrophoresis [128–130,179,1854], coupled with mass-spectrometry [1935], capillary zone electrophoresis [131], isotachophoresis [178,1906], and micellar electrokinetic capillary chromatography (MECC) [132]. However, not all these techniques are yet used in routine analysis. The development of biosensors [133] and chemical sensors [134] for specific substances was also reviewed. Other techniques use specific electrodes, such as for inorganic species [135] or organic substances, like theophylline [136], and there are radiochromatographic methods [137,138]. Microelectrodes are also increasingly popular [1933]. High performance ion chromatography (HPIC) [139], affinity chromatography (IAC) [140], and size exclusion chromatography [141], are now available for analytical toxicology purposes.

Spectroscopic methods other than mass spectrometry and other methods

Most spectroscopic methods can only be used to examine pure compounds. Many standard publications are available [142–144]. GC-Fourier transform-IR analysis of drugs was investigated [143]. A very comprehensive work in five volumes has been published by Mills et al. [145] and it provides reference spectra for the UV, IR, NMR and MS analysis of 1,400 drugs. This information can also be useful after chromatographic separation. Atomic absorption spectrometry (AAS), atomic emission spectrometry (AES) and flame emission spectrometry (FES) [146], plasma emission spectrometry [147] and X-ray spectrometry [148] have all been reviewed recently. Molecular fluorescence, phosphorescence and chemiluminescence spectrometry were reviewed [149] as well as inductively coupled plasma mass spectrometry (ICP-MS) [150], and nuclear magnetic resonance (NMR) spectroscopy [151,152,2053]. Drug-receptor interactions can be studied by multidimensional NMR [153]. For trace analysis, surface analysis techniques like Secondary Ion Mass Spectrometry (SIMS) [178] and other techniques may be used [154–155,2054].

Chemical sensors are becoming more popular [2055]. The activity of many drugs is well recognized to be dependent on the stereochemical constitution and a biologically active chiral molecule may have different potency, pharmacological action, metabolism, toxicity and pharmacokinetics. Enormous efforts have been paid to the separation of stereoisomers, for example enantiomers and

diastereoisomers. Chiral separation is either now available or is being investigated for many substances. Basically, stereoselective separations include either a chiral mobile or stationary phase in HPLC or GC, or a chiral derivatizing agent which essentially allows to keep the same chromatographic system as shown by a few illustrative examples [156–161,1832].

Extraction methods

Various extraction techniques are used for organic non-volatile substances, namely liquid-liquid extraction (LLE), solid phase extraction (SPE), and supercritical fluid extractions (SFE or SCF). It is noteworthy that direct injection of biological fluids into an HPLC column can be done without precipitation and column plugging, by the use of micellar mobile phases [162].

Liquid–liquid extraction techniques. This is a classical extraction technique using one solvent or a mixture of solvents that are not miscible with water, so that the extraction of organic compounds can be carried out at different pH values (namely acid, neutral and basic or so called amphoteric drugs) [23,31, 163,164]. This is a rapid, simple and not too expensive method, but it has the disadvantage of emulsion formation and great volumes of solvents.

Solid-phase extraction techniques. The analytes are fixed on a solid support during the first step (diatomaceous earth, ion-exchange, or a mixture of several materials) and then eluted during the second step. Reviews were published [165170,1834]. The reusability of columns was also studied [1607].

Supercritical fluid extraction techniques. The use of gases such as carbon dioxide in their supercritical region, allows the extraction of many organic molecules from biological materials and subsequent direct analysis by chromatographic techniques. A similar technique is also used for the decaffeination of coffee. Many recent papers are available [171–176].

MONOGRAPHS ON CHEMICAL SUSTANCES

Many substances will be covered in the following sections. Some may not be of primary concern for acute poisonings. Sometimes it may be necessary to quantify substances and it is useful to have at least one literature reference. In most cases, analytical methods still need to be adapted to the specific problem under investigation. In many cases, blood levels do not correlate well with toxic effects so that clinical assessment is often more reliable.

Food and drug additives and foodborne poisonings

Many foodborne poisonings are caused by bacterial, viral, protozoal or other gastrointestinal parasites. They are normally not handled by toxicology laboratories, but by microbiology laboratories instead. Recent papers on microbiological methods are proposed as examples [180–192]. The bovine spongiform

encephalopathy (BSE) is another matter of concern even though the causal agent (prion or bacterium) has not yet been clearly and definitely identified [1963].

Apart from mushroom poisonings and frequent hypersensitivity and intolerance reactions to food additives or ingredients [193–196], and accidental adulterations or contaminations of food [197–199], human poisonings related to food, food additives and drug additives, such as impurities in tryptophan leading to eosinophilia myalgia syndrome (EMS) [200], are sometimes described. Food and drugs are actually quite safe and the dietary intake of chemical contaminants is fairly small [201-203]. Examples of human poisonings have been reportedly due to glycyrrhizic acid from licorice [204,206], solanine from potatoes [207,208], to accidental poisoning with "deadly nightshade" (209), phototoxic burn following celery ingestion [210], kidney bean poisoning [211,212], erucic acid [213], borate, [214,1940] sulphiting agents [215–217], nitrites and nitrosamines [218]. A dramatic mass poisoning in recent years was known as the "Toxic Oil Syndrome" in Spain. The analytical toxicology was particularly difficult and the definitive causative agent could not be identified [225,226,2059]. The methanol contamination of wine in Italy was another example which had dramatic consequences [227], but formate could be monitored in the urine of patients [228].

Normally, substances from food cannot be detected easily in human specimens, except when high amounts are concerned. In most cases, the analysis of suspected food should be referred to food inspection laboratories [219–223]. It is now possible to quantify many food additives, for instance vitamins like niacin [1768] or vitamin A. Recently, some concern for pregnant women has arisen with vitamin A from calf liver [94,229–232]. Another cause for concern came from artificial sweeteners which can be easily detected in food [233–235]. Food poisoning by the rodenticide tetramine was reported in China [1781]. Methyl isothiocyanate, another contaminant in wine, was investigated by Uchiyama et al. [1798].

Naturally occurring toxicants

Many toxic plant components belonging to different chemical families are known or are being investigated. They include pyrrolizidin alkaloids, cyanogens, glycoalkaloids, lupin alkaloids, glucosinolates (which do hydrolyse to isothiocyanates), coumarins and furocoumarins, saponins, vicine and convicine, isoflavones, tannins, hemagglutinins, hydrazines, methylene dioxybenzenes, polyacetylenic compounds, ricin, many enzyme inhibitors, glyzirrhizin, hydrazones, methylxanthines, and toxic aminoacids. Some may be toxic and constitute a risk for acute poisoning. Very few analytical data relating to such poisonings in man are available. Comprehensive reviews on plant toxins have been published, including references on analytical methods [236,237]. One specialty section of the American Association of Official Analytical Chemists is dealing with analytical problems related to plants toxins [238].

The following recent examples have been found in the literature: cyanogenic glycosides has been extensively discussed by WHO [239]. The analysis of 5-vinyl-1,3-oxazolidine-2-thione (5-VOT), a goitrigenic compound obtained by enzymic degradation of progoitrin, one of the major glucosinolates from rapeseed meal, was performed by HPLC [240]. Scopolamine poisonings were investigated [241,242] and one case of colchicine poisoning was reported [243]. An interesting field of research is devoted to plant toxins used as arrow poisons for hunting by "primitive people" [244–246].

With the "green" trend of the Western civilization, herbal drugs have become very popular and many problems arose such as those due to impurities in Chinese herbs [104,247–251,2060]. An especially dramatic situation in young women using Chinese herbs was described including analytical toxicology [253]. Slimming regimens, Chinese black pills, ginseng, "rainbow pills", and other materials have been described [254]. A TLC method for the detection of coumarins and flavonoids [255], and methods for the determination of methoxsalen have been discussed [256,257]. Arecanut (Betel) chewing is popular in some countries [258] and poisoning with *Laburnum* species was described [259]. Cases of human poisoning by Philodendron [260], *Atractylis gumnifera* [1820] and *Taxus baccata* [261,262,1819] have been commented upon. Anaphylaxis following the ingestion of *Psyllium* was reported [263].

Analytic methods for the determination of coptisine, berberine and palmatine by capillary electrophoresis [264], determination of ricin by IA [265], atropine [266,1811], aconitine [267,268,1812], veratrine [269] and strychnine [270,1821,2061] have been described. The analysis of taxol, a complex diterpene from *Taxus brevifolia* used as antineoplastic agent, was described [271, 272,2062,2063]. One case of camphor poisoning was reported [273] and a method for gossypol in plasma [274].

Phycotoxins. Concern has been raised in the recent years by acute poisonings by amnestic, diarrhoeic and paralytic shellfish toxins (ASP, DSP and PSP toxins), as well as ciguatera and fresh water algae toxins (microcystins). The ASP toxin is known as domoic acid. PS-toxins are also known as saxitoxins. These toxins can be assayed by mouse bioassays, immunoassays and HPLC methods [275–282,1795]. Recent comprehensive reviews on seafood toxins have been published [283–285].

Mycotoxins. A very large number of papers have been published in recent years on this very exciting subject of considerable interest for health. These substances are probably among the most serious biological hazards to mankind unless an efficient protection of crops against molds can be implemented. Analytical methods were reviewed [286–289,2064].

The most toxic mycotoxins are found in the aflatoxin family and literally thousands of papers have been published on this subject (e.g. [290–298]). Papers on ochratoxin [299–302,2065,2066], patulin [303], cyclopiazonic acid [304], fusarochromanon mycotoxins [305], fumonisins [306,307], trichothecenes [308] and wortmannin [309] were also published.

Mushrooms. The analytical and clinical toxicology of mushroom poisonings

and mushroom toxins were recently reviewed [310–314,2204,2209]. Assays of orellanine [315] and the role of the clinical laboratory in *Amanita virosa* poisoning [316] have been discussed as well as the conformation of viroisin, a monocyclic toxic heptapeptide of the virotoxin family [2158].

Animal toxins. Routine analytical toxicology laboratories seldom deal with these toxins, but it may be of interest to have at least some references available to deal with this problem, if it occurs. A HPLC method for bee venom was discussed [317]. Snake venoms were reviewed [318,319,1769]. The quantification of cantharidin in human serum was discussed [320]. A more general approach to animal toxins was covered by Mebs [321,322]. Fish toxins such as tetrodotoxin were discussed by Japanese authors [323–325]. The determination of aliphatic amines and histamine as the causative toxins of scombroid fish poisoning was also discussed [326,327]. Laboratory findings in one case of acute toxic renal and hepatic failure after ingestion of raw carp bile were commented on [328].

Drugs acting on the nervous system

Psychotropic drugs

Barbiturates. As the majority of barbiturates are somewhat out of therapeutic use (with some exceptions), few recent papers are available on analytical toxicology [329,330] and classical articles or textbooks are recommended [23, 25,28]. Barbour [331] reported a derivatizing agent for the propylation of fairly polar barbiturates to obtain improved chromatographic behaviour. Pocci et al. [332] investigated the solid-phase extraction and GC/MS confirmation of barbiturates in urine. Papers on crotylbarbital pharmacokinetics [333], a LC-MS technique for heptabarbital [334] and the metabolism of propallylonal [335] were published. Pharmacokinetic data are summarized in Table 2.4.

Benzodiazepines. The major source of information on analytical techniques was published by Schütz [340,341]. The chromatography of benzodiazepines was also been extensively reviewed by Siouffi and Dubois [342] who covered general as well as individual assays using thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), gas chromatography (GC) with different detectors and gas chromatography–mass spectrometry (GC-MS) for the following classes of benzodiazepines (with their major metabolites): 1,4-benzodiazepines (bromazepam, camazepam, chlordiazepoxide, clonazepam, diazepam, chlorodesmethyldiazepam, dipotassium chlorazepate, ethyl loflazepate, flunitrazepam, flurazepam, halazepam, lorazepam, lormetazepam, medazepam, nitrazepam, oxazepam, pinazepam, prazepam and quazepam); 1,5-benzodiazepines (clobazam); imidazo-1,4-benzodiazepines (climazolam and midazolam); triazolobenzodiazepines (adinazolam, alprazolam, brotizolam and triazolam) and thienodiazepines (clotiazepam). Since then, numerous papers have appeared in the literature as benzodiazepines are widely used as tranquillizers and for other purposes. Pharmacokinetic data are summarized in Table 2.5.

Methods used to assay benzodiazepines in biological fluids are extremely

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/L) Therap. range	 Toxic range	Ref.
Allobarbital		40–48		5–20	>30	75
Amobarbital		15–40	0.9–1.4	1–8	>10	75,336,339
Aprobarbital		13–34		4–20	>30	336,338
Barbital		48	0.4–0.6	10–40	>60	75,336
Brallobarbital		20–40		5	10	336,338
Butalbital		30–88		1.0–5.0	>10	75
Butobarbital = Butethal		38	0.8	1–5	>10	75,339
Cyclobarbital		8–17	0.5	2.0–6.0	>10	25,336,338
Heptabarbital		6–11	1.0	0.5–5	>10	25,336,338
Heptobarbital				50–100	125–150	336
Hexobarbital		3–7	1.1–1.3	2–10	>15	25,34,337
Metharbital				5		25
	Barbital	48	0.4–0.6	10–40	>60	75,336
Methohexital		1–4	1.0–2.2	1–6	>100	25,75,339
Methylphenylbarbital = Mephobarbital		48–52	2.6	2.5–3.5	40–60	75
	Phenobarbital	48–144	0.5–0.7	15–40	40–60	75,339
Pentobarbital		15–48	0.5–1.0	1–4(25–40)*	>5	25,75,339
Phenobarbital		48–144	0.5–0.7	15–40	40–60	75,339
Propallylonal		~3		0.3–10	>10	338
Secbutabarbital = Butabarbital		34–42		5–17	>20	75,338
Secobarbital = Quinalbarbital		22–29	1.5–1.9	1–5	5–12	75,339
Vinylbital		18–33	0.7	1–3	>5	25

*In traumatic patients.

***Table 2.4**. Barbiturates*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Adinazolam		2–3				369,370
	Mono-Desmethyladinazolam					
Alprazolam		6–20	0.9–1.5	0.005–0.08	0.1–0.4	75,338,375
	4-Hydroxyalprazolam					
	Alpha-Hydroxyalprazolam					
Bromazepam		8–20	0.9	0.08–0.17	0.25–0.50	25,336,340
	3-Hydroxybromazepam					
Brotizolam		3–10	0.7	0.001–0.03		45,338,339
	4-Hydroxybrotizolam					
Camazepam		20–24		0.1–0.6	2	336,338
	Temazepam	5–15	0.8–1.5	0.2–0.9		
Chlordiazepoxide		5–30	0.3–0.7	0.7–4.5	3.5–10	337,340
	Desmethylchlordiazepoxide			0.3–3.5		
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Demoxepam			0.2–3.8		340
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
Clobazam		10–77	0.9–1.8	0.1–0.4		36
	N-Desmethylclobazam	36–46		0.5–4		36
	4-Hydroxyclobazam					
Clotiazepam		2–18	0.8–1.7	0.1–0.7		338,347,380
	N-Desmethylclotiazepam	5				
	Hydroxyclotiazepam					
Cloxazolam						
	Delorazepam	48–244	2.2	0.01–0.07		340
	Lorazepam	10–25	0.9–2	0.02–0.25		340
Delorazepam = Chloronordazepam		48–244	2.2	0.01–0.07		45,340,377
	Lorazepam	10–25	0.9–2	0.02–0.25		340
Demoxepam				0.3–2.8	1	45,337

	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
	N-Desmethyldemoxepam					
Diazepam		15–60	0.7–2.6	0.5–0.75	1.5–3.0	45,336
	Temazepam	5–15	0.8–1.5	0.2–0.9	>1	336,340
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75
Dipotassium Chlorazepate		1–3	1.1–1.7	0.02		36,337
	Nordazepam	30–100	0.7–2,.5	0.1–0.8	1.5–2	40,336,339
Estazolam		8–31		0.07–0.8	>1	340,384
Ethyl Loflazepate		67–120		0.02–0.2		340
	Descarboxyloflazepate					
	N-Desalkylflurazepam	70–120		0.04–0.15	>0.3	340
Fludiazepam						340
	N-Desalkylflurazepam	70–120		0.04–0.15	>0.3	340
Flumazenil (=antagonist)		0.5–1.3	0.6–1.6	0.03–0.7		340
Flunitrazepam		10–35	3.4–5.5	0.005–0.015	0.05–0.1	75,336,1838
	N-Desmethylflunitrazepam			0.001	0.01	1838
	7-Aminoflunitrazepam			0.002	0.04	1838
	3-Hydroxyflunitrazepam					
	7-Acetamidoflunitrazepam					
Flurazepam		2–3		0.001–0.02	>0.2	75,337
	N-Desalkylflurazepam	70–120		0.04–0.15	>0.3	340
	N-Hydroxyethylflurazepam	0.9–5				340
Halazepam		14–16		0.04		340
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
Ketazolam		1–5		0.004–0.2		340
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75
Loprazolam		4–10		0.005–0.01		340
Lorazepam		10–25	0.9–2	0.02–0.25	0.3–0.6	336,340
	Hydroxylorazepam					

Table 2.5. *Benzodiazepines (continued overleaf)*

Compounds	Main metabolites	Elim. half-time	V_D	Plasma (serum) conc. (mg/l)		Ref.
Parent drug		(h)	(l/kg)	Therap. range	Toxic range	
Lormetazepam		10–12		0.002–0.025		336,340
	Lorazepam	10–25	0.9–2	0.02–0.25	0.3–0.6	
Medazepam		1–5	0.4	0.01–0.5	>0.6	336,340
	Diazepam	15–60	0.7–2.6	0.5–0.75	1.5–3.0	
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
Metaclazepam		17–30		0.05–0.2		340
	N-Desmethylmetaclazepam			0.02–0.04		340
	Bis-Desalkylmetaclazepam					
Midazolam		1–4 (I.V. 22)	0.8–2.5	0.08–0.25		336
	4-Hydroxymidazolam	0.8–5.4				340
	Alpha-Hydroxymidazolam					
Nitrazepam		18–30	2–5	0.03–0.12	0.2–0.5	340
Nordazepam		30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	340
Oxazepam		4–25	0.7–2.3	0.2–2	2–8	340
Oxazolam		1–5		0.05–0.2		338
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
Pinazepam		12–15		0.01–0.05		340
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
	N-Desalkylpinazepam					
	3-Hydroxypinazepam					
Prazepam		1–3	12–14	0.05–0.2		336,338
	Nordazepam	30–100	0.7–2.5	0.1–0.8	1.5–2	40,336,339
	3-Hydroxyprazepam					
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
Quazepam		31–74		0.01–0.05		45,340

	2-Oxoquazepam					
	N-Destrifluoroquazepam					
Temazepam		5–15	0.8–1.5	0.20–0.90	>1	336,340
	Oxazepam	4–25	0.7–2.3	0.2–2	2–8	75,338,339
Tetrazepam		10–26	0.8–1.6	0.05–0.7	>1	340
	Nortetrazepam	30–42				340
Tofisopam		2.7–3.5				45,1979
Triazolam		1.5–5.9	0.8–3.9	0.002–0.020		337,340
	4-Hydroxytriazolam	3–8				1778
	Alpha-Hydroxytriazolam	3–8				1778

Table 2.5. *Benzodiazepines*

varied. Some are specific, others are not, like the immunoassays. For screening purposes, it is advisable to combine immunoassays with chromatographic techniques, as currently available immunoassays are unable to discriminate between the different benzodiazepines due to the cross-reactivity of antibodies. This may have some advantages, but also one major drawback, namely that it cannot be decided whether a pharmacologically very potent or less toxic compound of the same family is involved or both. The use of radioreceptor assays [343] and a non-isotopic receptor [344] were discussed. The kinetics of acute poisonings with several benzodiazepines were reviewed [345–349,1988]. The problem of endogenous benzodiazepines was discussed by Mullen et al. [350]. HPLC screening methods with different detection systems [351–357,1930, 1782,2068], immunoassays [358–360,1910,2069], and the use of benzophenone derivatives [361–363] were considered by numerous authors, as well as other techniques like LC-MS [364] and GC-MS [365,366,2070,2195].

The problem of "false negatives" was discussed [367,2031,2034,2037,2038] and a general bibliography on benzodiazepines published by Sunshine [368]. Other workers have been interested only in individual substances like adinazolam [369–371], alprazolam [372–375], brotizolam [376], chlordesmethyldiazepam [377], clobazam [378], clonazepam [379], clotiazepam [380], diazepam [381,382], estazolam [383,384], ethyl loflazepate [385], etizolam [386], flunitrazepam [1838], flurazepam [387], halazepam [388], midazolam [389–393,2071], nitrazepam [394], oxazepam [395], pinazepam [396], quazepam [397,398], temazepam [399,400], tetrazepam [401], tofisopam [1979] and triazolam [402,403,2072].

The hydroxylated metabolites of alprazolam and triazolam were assayed [404] and triazolam concentrations in forensic cases of impaired driving were studied[402]. The benzodiazepine antagonist flumazenil can also be monitored, if required [405,2071,2073].

Non-barbiturate hypnotics and sedatives. The same comments as for barbiturates can be made on substituted ureas or monoureide hypnotics, and other non-barbiturates that are rarely seen nowadays in acute poisonings.

Monoureide hypnotics: A recent method for the simultaneous determination of thermolabile monoureides, like bromvaleryl-urea (bromisoval), bromodiethylacetyl-urea (carbromal), and allylisopropylacetyl-urea (apronal) by HPLC and TLC has been described [406]. Another method using wide bore capillary GC was discussed for the quantification of bromisoval [407]. Steinhoff et al. [408] discussed chronic poisonings with these compounds.

Carbamates: no really new derivatives have been introduced and only a few papers have recently been published, such as on carisoprodol [409]. For meprobamate, phenprobamate, ethinamate and hexapropymate, the classical literature [23,28,31] or more recent papers [329,410] can be recommended.

Quinazolones: The "old drugs" methaqualone and mecloqualone are nowadays rarely seen in overdoses, except in South Africa, India and a few other countries, where they are still heavily abused. A recent paper on an immunoassay was published [412].

Piperidinediones: Methyprylon [413] and glutethimide [414–416] are now of historical interest only. They formerly played a role as "KO drops" in red-light districts, where they have been substituted for by flunitrazepam, triazolam or similar drugs [417,418].

Aldehydes: Paraldehyde [419] and chloral hydrate [420–425,2066], which is converted to trichloroethanol, are only rarely seen in overdoses. The same is true for α-chloralose, which is also used as a rodenticide [426].

Ethchlorvynol: This drug is occasionally seen in intensive care units and morgues [427–429].

Miscellaneous "old" sedative hypnotics. The famous teratogenic drug thalidomide has only historical interest, even though new therapeutic uses are emerging [430]. Clomethiazole, which is used mostly in the treatment of alcohol withdrawal, can be monitored by HPLC [431]. Buspirone can be detected and quantified by HPLC [432].

Miscellaneous "new" sedative hypnotics. Gamma-aminobutyric acid ([ABA] can be monitored [433,2067] as well as alpidem and zolpidem [434–438,1771]. Suriclone and zopiclone can be assayed by HPLC or other techniques [438–442,1796,1846,1962]. Ritanserin, a serotonin antagonist, used for the treatment of insomnia and withdrawal symptoms in chronic alcoholics, can be monitored by GC-MS [443–445]. Centbutindole and its metabolite can be assayed by HPLC [446]. Pharmacokinetic data are summarized in Table 2.6.

Antipsychotics

Phenothiazines and azaphenothiazines. Phenothiazines have been reviewed by several authors [447,448,1772]. The metabolism of several phenothiazines was investigated by Choo et al. [449]. A determination of thioridazine and its metabolites in serum [450] and the light-induced racemization of diastereoisomer pairs of thioridazine-5-sulphoxide [451] were also studied. The metabolism and pharmacokinetics of levomepromazine [452], prochlorperazine [453] and chlorpromazine [454] were described. Prothipendyl can be quantified by HPLC [436]. Pharmacokinetic data are summarized in Table 2.7.

Butyrophenones. Brandenberger et al. [455] published a convenient mass spectrometric method for low concentrations of butyrophenones. Haloperidol and its reduced metabolite RH can be assayed by various methods [456–460]. Park et al. [461] described a HPLC method for biological fluids and tissue homogenates. Azaperone and its metabolite dihydroazaperone were identified in the urine of a poisoned patient [462]. Screening for haloperidol together with other neuroleptics by HPLC/DAD or HPLC/ECD has been discussed [448, 2074]. The other butyrophenones include benperidol [463], droperidol [464], fluanisone, melperone, moperone, pipamperone [465,466] and trifluperidol.

Diphenylbutylpiperidine derivatives. Screening for fluspirilene, penfluridol, and pimozide was also described [448,467].

Thioxanthenes. Thiothixene is detected by LC-EC [468]. The cis or Z-clopenthixol is the pharmacologically active isomer. It can be assayed by HPLC

Compounds	Main metabolites	Elim. half-time	V_D	Plasma (serum) conc. (mg/l)		Ref.
Parent drug		(h)	(l/kg)	Therap. range	Toxic range	
Acecarbromal				10–20	>25	336
Alpidem				0.05		438
Bromisoval				10–20	30–40	337
Buspirone		2–11	5.3	0.001–0.004		36
Carbromal		7–15		5–10	15–20	336
Carisoprodol		8	0.6	0.2–30	50–100	34
Chloral Hydrate		4–5 min				
	Trichloroethanol	6–10	0.6	1.5–15	40–70	75
	Trichloroacetic Acid	67				75
Clomethiazole		3–5	4–15	0.1–0.8	10–80	75
Diethylpentamide		6–7		2–10	20	338
Ethchlorvynol		19–32	2.4–3.2	0.6–1.8	>20	45
Ethinamate		2.3	1.6	1–6	100–200	45
Glutethimide		5–22	2.7	5–10	20	75
Hexapropymate				2–5	10	336
Hydroxyzine		2.5–20	22.5	0.05–0.09	>0.1	45
Meprobamate		6–17	0.7	10–20	50–100	75
Methaqualone		20–60	6	1–3	5–8	75
Methyprylone		9–11	0.97	10–	>50	45
Paraldehyde		3–10	0.9	30–300	100–400	336
	Acetaldehyde			0–30	100–125	336
Pyrithyldione		–20		1–10		338
Ritanserine		10–60		0.05–0.12	20	445
Valnoctamide				5	40	337
Zolpidem		2–4.3	0.5	0.1–0.2	>3	45,436,438
Zopiclone		3.5–6	1.4	0.06–0.07	0.15	337,438
	N-Desmethylzopiclone					

Table 2.6. *Anxiolytics–hypnotics–sedatives*

Compounds	Main metabolites	Elim. half-time	V_D	Plasma (serum) conc. (mg/l)		Ref.
Parent drug		(h)	(l/kg)	Therap. range	Toxic range	
Alimemazine = Trimeprazine		3.6–7		0.05–0.4	>0.5	36,337
Butaperazine		5–33		0.07–0.7		75
Chlorpromazine		30	7	0.05–0.3	0.5–1	36,45,337
Cyamemazine				0.05–0.4	9.8	84
Fluphenazine		3–45		0.005–0.025	0.05–0.1	337,338
Levomepromazine = Methotrimeprazine		15–30	23–42	0.03–0.15	0.5	36,336
Perazine				0.025–0.1	0.5	337
Pericyazine				0.005–0.03	0.1	337
Perphenazine		9.5	20–25	0.001–0.02	0.05	36,336
Pipothiazine		15–16d		0.001–0.06	0.1	36,336
Prochlorperazine		0.2–13	23	0.01–0.04	0.2–0.3	36,336
Promazine				0.1–0.4	2–3	336
Promethazine		7–14	9–18	0.1–0.4	1–2	36,337
Prothipendyl				0.1–.0.2		436
Thioridazine		16–36	10–18	0.2–1	>1	36,75,336
	Mesoridazine	2–9	3–6	0.1–1.5	3–7	75
	Sulforidazine				0–0.5	75
Trifluperazine		7–18	160	0.005–0.05	0.1–0.2	36,336
Triflupromazine				0.03–0.1	0.3–0.5	336

Table 2.7. *Phenothiazines*

[469]. Flupenthixol can be assayed by RIA and GC [470–472]. Chlorprothixene at trace levels can be measured by voltametry [473].

Other antipsychotics. They include amisulpride [474,475], raclopride [476], sulpiride, sultopride [477,478], tiapride and clozapine [479–482]. The pharmacokinetics and pharmacodynamics of clozapine were discussed by several authors [483–485]. Remoxipride can be assayed in plasma by HPLC with UV detection [486–488,1982]. Risperidone and 9-hydroxyrisperidone can be monitored in plasma by HPLC [489]. Pharmacokinetic data are summarized in Table 2.8.

Antidepressants

Many severe poisonings are due to antidepressants (as reviewed in Chapter 7 of this volume). Therefore any toxicology laboratory should be able to monitor a number of members of this family which now includes many more substances than the mere tricyclic antidepressants [2048,2075,2076]. Asselin et al. investigated the use of serum EMIT assays for the analysis of urine samples [490] as well as the use of serum tests for hemolyzed whole blood [491]. An evaluation and comparison of the results of some immunoassays was performed [492]. The specificity of data for tricyclics in FPIA was also investigated. [1792,2077].

Many other compounds with a similar structure, such as the phenothiazines [2078], several antipsychotics, and carbamazepine in toxic amounts do cross-react with tricyclics in most immunoassays, which can lead to erroneous conclusions if no correct interpretation of results is made and if the involved substances have not been identified [1792]. Diphenhydramine at high doses also interferes [493]. The same can be said for cyclobenzaprine, a centrally acting relaxant with similar structure, in HPLC [494]. Gas chromatographic separation of tricyclics was investigated [495] and various HPLC methods have been reviewed [496–500]. Salomon et al. [501] separated antidepressants by capillary electrophoresis and Lee et al. [502] did this by electrokinetic capillary chromatography.

Several authors have focused on the pharmacokinetics of antidepressants [503–510]. As regards antidepressants individually, the following alphabetical list is not an exhaustive survey. Amineptine is very difficult to assay in body fluids as it has both a basic and an acidic function. In addition, it easily breaks down into many metabolites [511,512]. Concern arose because of amineptine abuse [514], in contrast to most other antidepressants which are not abused. Amineptine can be assayed by HPLC [515]. One case of amoxapine suicide was investigated [516]. The plasma determination and toxicology of bupropion were studied by several authors [517–520,2143]. An assay and a review of the pharmacology of citalopram were published [521–523]. Different methods for clomipramine were proposed [524–526,2191]. The metabolic interaction of clomipramine and ethanol was elucidated [527]. Kreamer-Nielsen et al. [528] studied clomipramine pharmacokinetics and Dale et al. [529] reported on a near-fatal overdose. The determination of desipramine and metabolites in

Compounds	Main metabolites	Elim. half-time	V_D	Plasma (serum) conc. (mg/l)		Ref.
Parent drug		(h)	(l/kg)	Therap. range	Toxic range	
Bromperidol				0.002–0.02		336
Chlorprothixene		8–12	10–22.7	0.03–0.3	0.7	336
	Chlorprothixene Sulphoxide					
Clopentixol = Zuclopentixol		13–23	20	0.005–0.05	0.15–0.3	36,336
Clotiapine=Clothiapine=Clotiapin		10	1			2029
Clozapine		12		0.2–0.6	0.8–1.3	36
Droperidol		2–3	1.7			45
Flupentixol		35	14	0.001–0.015		45,337
	Flupentixol Sulphoxide					
Fluspirilene				0.003		336
Haloperidol		10–40	17–29	0.005–0.04	0.05–1	36,75,337
	Reduced Haloperidol					
Loxapine		3–4		0.005–0.01	>0.2	45,75
Pimozide		18–150	0.2	0.001–0.2		34,45,336
Pipamperone				0.1–0.4	0.5–0.6	336
Raclopride		9–19	0.1–2.1	0.02–0.2		476
Remoxipride		4–7	0.7	0.2–1.5		36,1982
Sulpiride		6–8	0.6–1.4	0.04–0.6		36,337
Sultopride				0.1–1		477
Thiothixene		34		0.001–0.025	0.1	337

Table 2.8. *Other antipsychotics*

serum [530,531] and the more classical drug dothiepin were investigated [532–534]. The cis- and trans-isomers of doxepin were measured in plasma [535] and its stereoselective pharmacokinetics investigated [1949]. The newer antidepressant fluoxetine and its metabolite norfluoxetine were assayed by HPLC/DAD [536–540,2192,2193]. The importance of the collection site was stressed[543]. Fatal poisonings due to fluoxetine [541,542] and a possible (anecdotal?) association between fluoxetine use and suicide [544] were reported. The recent antidepressants clovoxamine and fluvoxamine were monitored in human plasma [545,546,2086]. Pharmacokinetic studies dealing with the interaction of fluvoxamine with imipramine/desipramine [548] or in patients with liver cirrhosis [549] were published. Serotonin can also be measured in plasma [547].

The analytical methodology concerning imipramine [550], levoprotiline [551], lofepramine [531,2079], loxapine [552], maprotiline [553] was studied. Hundt et al. [554] used an automated HPLC-method with electrochemical detection to monitor mianserin in plasma. Enantiomeric separations of mianserin and metabolites were performed [2080]. Several Japanese authors studied the metabolism and side-effects of mianserin in relation to plasma concentrations [555–557]. Nomifensine led to acute poisonings and side-effects, and was withdrawn from the market [1957]. Papers were published on analytical methods and the pharmacology of nortriptyline [558], oxitriptan [559], paroxetine [560,561,2194], quinupramine [562], reboxetine [1905,2196]. Sertraline was investigated by several researchers [563–567,2081]. The pharmacokinetic profiles of tianeptine in the rat [1978] and a HPLC-method [1991] were investigated. Several authors studied trazodone [568,569,2197]. The plasma levels of trimipramine and its metabolites [570,571] and the quantitation and pharmacokinetics of tryptophan were investigated [572–574]. Analytical methods and the pharmacokinetics of viloxazine [575–577] and venlafaxine [2082,2220] were studied. An interesting debate on the monitoring of biological markers in "suicidal" patients is going on [578–580,2198]. Pharmacokinetic properties of antidepressants and MAO-inhibitors are summarized in Tables 2.9 and 2.10.

A- and B-type monoamine oxidase inhibitors (MAOIs). The first generation of MAOIs for which analytical methods are available, e.g. iproniazide [581], isocarboxazide [582], nialamide, phenelzine [583,1813], and tranylcypromine [584,585,1816] are not longer commonly used in many countries because of severe side-effects. These substances are seemingly back and hence are more frequently involved in acute poisonings. A new generation of MAOIs has appeared including brofaromine [2083], lazabemide [2084], clorgiline, selegiline, pargyline, iproclozide, and moclobemide [2085].

Lithium. The analytical toxicology of lithium is not very complicated. Recent papers [586–588] have been published.

Compounds	Main metabolites	Elim. half-time	V_D	Plasma (serum) conc. (mg/l)		Ref.
Parent drug		(h)	(l/kg)	Therap. range	Toxic range	
Amineptine		0.8–5.3	2.4	0.6–2.6		511,512
	C5-Metabolite	2–9		0.25–1.2		511
Amitriptyline		10–30	12–16	0.05–0.2	>0.5	336,338,507
	Nortriptyline	22–68	17–31	0.05–0.25	>0.5	
Amitriptylinoxide						
	Nortriptyline	22–68	17–31	0.05–0.25	>0.5	337
Amoxapine		8–30	1148	0.2–0.4		34,339
	8-Hydroxyamoxapine					
Bupropion		8–24	1.4–32	0.025–0.1	11–21	36,517
Butriptyline				0.07–0.15	0.4–0.5	336
Citalopram		33	14	0.01–0.2		507,521,523
	Desmethylcitalopram			0.01–0.1		521
	Didesmethylcitalopram					
	Citalopram-N-Oxide					
Clomipramine		20–40	17–25	0.02–0.15	0.4–0.6	338,339
	Desmethylclomipramine			0.1–0.2	0.3–0.4	338,339
Desipramine		10–30	18–42	0.03–0.3	>0.5	34,338
Dibenzepin		5		0.05–0.25	>3	75,338
Dothiepin = Dosulepin		11–40	20–92	0.05–0.2	>0.8	338
	Northiaden	22–60		0.1–0.2	0.5–0.75	36,337
Doxepin		8–25	9–33	0.05–0.25	>0.5	75,338
	Nordoxepin	33–80		0.1–0.25	>0.5	75
Fluoxetine		48–72	20–42	0.02–0.05		339
	Norfluoxetine	ad 140		0.15–0.5		
Fluvoxamine		7–62	5	0.05–0.2		36,336
Imipramine		6–26	28–61	0.05–0.3	>0.5	36
	Desipramine	10–30	18–42	0.03–0.3	>0.5	34,338

Table 2.9. *Antidepressants (continued overleaf)*

Compounds	Main metabolites	Elim. half-time	V_D	Plasma (serum) conc. (mg/l)		Ref.
Parent drug		(h)	(l/kg)	Therap. range	Toxic range	
Lofepramine		4–17		0.003–0.01		338
	Desipramine	10–30	18–42	0.03–0.3	>0.5	34,338
Maprotiline		20–60	23–70	0.05–0.25	>0.5	36,336
	Desmethylmaprotiline			0.1–0.4	0.75–1	
Melitracen		12–23		0.01–0.1		338
Mianserin		10–23	6–40	0.03–0.12	>0.5	339
	Desmethylmianserin				0.3–0.5	
Nomifensine (withdrawn)		2–5	6.5	0.02–0.07	0.8	34
Nortriptyline		22–68	17–31	0.05–0.25	>0.5	36
Opipramol		6–23	10	0.05–0.2	0.5	336,338
Paroxetine		3–65	3–28	0.001–0.15		36
Protriptyline		50–200	15–32	0.05–0.2	>0.5	336,338
Quinupramine		35				2027
Sertraline		24–26	~20	0.3		36
	Desmethylsertraline	62–104		0.2		
Tianeptine		3.3	1.2			45
Trazodone		1–8	0.7–1.3	0.3–1.7	>2	339
Trimipramine		10–40	31	0.02–0.2	>0.5	336,339
Tryptophan		1.8–2.2	0.3–0.7			572
	5-Hydroxytryptophan (5-HT) = Oxitriptan					
Viloxazine		2–5	0.5–1.5	0.5–5	45	25
Zimelidine (withdrawn)		5	1–5	0.01–0.14	>0.7	34,75
	Norzimelidine				>2	

Table 2.9. *Antidepressants*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Ipronazide		9–10				25
Isocarboxazide		2–36		<0.5		25,36,45
Moclobemide		2	1.1	0.2		45
Phenelzine		1–4.5		0.002	>1	36,45
Tranylcypromine		1.5–2.7	1.1–5.7	0.01–0.09	>3	75,585

***Table 2.10**. MAO inhibitors*

Addictive drugs

The testing of addictive drugs is a major area of activity in many toxicology laboratories. These tests are performed in acute overdoses as well as methadone detoxification and maintenance programmes, forensic applications and at the workplace. In the US, testing for addictive drugs at the workplace led to the mushrooming of private laboratories specialized in this field. Many controversial discussions on analytical toxicology have taken place in the past and continue today [589–601]. Some authors were interested in the detection of body packers [602,1869]. The US authorities, and in particular the National Institute on Drug Abuse (NIDA), now Health and Human Services (HHS), established minimum requirements for drug testing [591] to guarantee a nationwide quality of analysis. These requirements were recently updated [1912,2190].

The pharmacology of drugs of abuse has been summarized [1738] as well as the clinical pharmacokinetics of non-opiate drugs of abuse [594] but not much is actually known, as large-scale human experimentation is not ethically acceptable. As repression is becoming more effective in many countries, replacement drugs are coming up. These so-called "smart drugs" [1737] include piracetam, hydergine, vincamine, phenytoin, choline, vasopressin, amino acids, tacrine... They are served in "smart bars" with "smart drinks" (i.e. highly vitaminated drinks). Even the anesthetic/anticonvulsant drug tiletamine has been abused in the UK [411]. In 1991, the book "PIHKAL — A Chemical Love Story" [603] published by a pharmacologist from Berkeley University gave rise to a great concern. PIHKAL is an acronym for "Phenylethylamines I have known and loved" and the use of about 180 completely new designer drugs (mostly not prohibited by law) is recommended and detailed recipes for synthesis provided. Another similar book is in preparation [2087].

Driving under the influence of narcotic drugs, especially in combination with alcohol is another matter of concern [1849,1857,2088,2089].

A phenomenon totally unknown some years ago, is drug abuse in Eastern countries, for example Russia, where illicit ephedrone, methylfentanyl and methadone are heavily abused. Ephedrone has become a substantial drug of abuse in this country and has led to many overdoses [1837,1871]. Methcathinone, another illicit drug from Russia, is now available in the US [1943] and seems to have a potential for abuse as marked as that of cocaine.

Sampling. Great care should be exercized during the sampling and storage of body fluids [604], especially for cocaine [605] because blood esterases give rise to benzoylecgonine, a metabolite not easily detectable by the same method. The adsorption on the walls of plastic containers for cannabinoids is another example of concern in sample transport and storage [606,1888]. Drug addicts ingest cholinesterase inhibitors, like organophosphates, to prevent the metabolic breakdown of cocaine [1868]. It is also important to have representative samples of seized street drugs if quantitative assays or comparison of impurities to trace the original clandestine laboratories are performed [607–610,1934,2117].

Screening tests. Many screening procedures for drugs of abuse have been proposed [611–620,1840,1843,1870,1876,2090,2094,2203]. Attempts have been made to extend the use of immunoassays originally dedicated to urine analysis, to blood analysis and vice versa [615–618,1874,1898]. As many laboratories firstly use immunoassays [1851], great attention should be paid to adulterants [621,622,1790,1808,1908,1918,2032–2034,2040] and cross-reacting substances, especially with amphetamines [623–628,1900,1901]. These interferences are also observed in GC-MS when ephedrine or/and pseudoephedrine are present [629,630,1920,2039]. Other cross-reactivities were observed in methadone and phencyclidine tests by diphenhydramine OD [631,632]. Most herbal teas do not interfere with immunoassays [1789].

False-negative results may be obtained in GC-MS with benzoylecgonine if fluconazole [1931] is present in urine and the metabolite of methadone EDDP may not be detected by immunoassays [1936]. NSAIDs and ritodrine are also known to interfere in immunoassays for cannabinoids. Some NSAIDs also consume methylation reagents in GC-MS [633–636]. The antiemetic nabilone does not cross-react with cannabinoids [637], but dronabinol (= THC) does. False positive EMIT results have also been described [2038,2041].

Hair analysis and drug treatment programmes. Reviews on drug detection in hair have been published recently [638,639,2095–2100,2200–2202]. Other authors [640–642,1776,1777,1850] have also been concerned with this field of growing interest, since it is known that knowledgeable drug addicts can easily avoid positive urine samples [726] especially addicts in methadone treatment programmes. There also seems to be a relation between the administered dose of methadone (l and d,l forms are commercialized) and the concomitant use of heroin and other drugs [643–646]. Many papers have dealt with the treatment of drug addicts [1858,1861] and AIDS, for instance the pharmacokinetic interaction of antimicrobial agents with methadone [725]. Möller et al. [1797] investigated the cocaine content in the hair of Bolivian coca chewers.

CNS stimulants ("uppers")

Amphetamine and its analogues are important drugs of abuse from the viewpoint of analytical toxicology. Testing is not easy as these compounds are very volatile, hence there is a loss due to evaporation during the concentration step, which can be avoided by adding small amounts of acid during the evaporation of extraction solvents. Several screening methods have been investigated [1879,1897,1899,1901]. Another challenge is the difficult problem of stereoisomers as some are active and some are not [647–651,2102]. It is also very difficult to distinguish amphetamine and derivatives from other sympathomimetic amines [1895,1896].

The metabolism of benzphetamine, dimethylamphetamine and furfenorex was investigated [652,658]. Amfepramone and its metabolites can be assayed by GC [653]. Cathinone, the active ingredient of "khat", was studied in body fluids [654–657]. Taylor-Noggle et al. [659] studied the stereoisomers of dimethylami-

norex, Van der Merve [660] fencamfamine and metabolites in urine, and Rücker et al. [661] the biotransformation of fenethylline. Caccia et al. [662] investigated the pharmacokinetics of fenfluramine, the only non CNS stimulant of this class, in volunteers and Segura et al. [739], the metabolism of mesocarb used for doping. Methamphetamine and the stereochemical and pharmacokinetic problems associated with analytical methods were addressed by several authors, including the selegiline story [663–667,911,1775,1894]. "Ice", the "poor man's cocaine", is a special form of methamphetamine [1736]. Impurities in street samples of amphetamines can be used to elucidate the synthetic pathways used in clandestine laboratories [1934]. Methylphenidate, another stimulant, was dealt with in a series of papers, including the metabolite ritalinic acid and stereoisomeric problems [668–672]. Phenmetrazine can be determined by GC [1009]. Sibutramine, a new weight control agent, has not yet been reported to be abused [673].

Cocaine. This old drug, abused for so many years, has shown up in a new and particularly toxic form, "crack" [674,675,1752–1755]. The neurobiology of cocaine was recently reviewed [1739]. Many analytical methods are available for blood as well as urine [676,678–680,1741,1742,2103]. The problem of passive inhalation of free base cocaine was discussed [678,1709,1766]. Ecgonine methylester, presumably a major metabolite of cocaine in humans, was studied [1927,1791]. A long discussion was conducted on the simultaneous ingestion of alcohol and cocaine leading to the formation of cocaethylene [1756–1761,2104]. Many other issues related to cocaine can be found in the recent literature for example pharmacokinetics [681,1747,1748], side effects [1751], adulteration by scopolamine [677] or benzococaine resulting in methemoglobinemia [1745], the use of coca-paste [1743], mate de coca herbal tea [1744], health Inca tea [1746], occupational exposure of criminal laboratory staff to cocaine [1749], contamination of currency by dealers [1750], and reproductive toxicity [1762–1767,2105–2108]. Pharmacokinetic data on CNS stimulants and anorectics are summarized in Table 2.11.

CNS depressants ("downers")

Opioids. Many opioids have been abused for a long time. It should be borne in mind that most immunoassays for opiates [682,683] do not detect the synthetic opioids. Opiates are the natural or semisynthetic phenanthrene or natural morphinane derivatives from poppy (*Papaver somniferum*). All the compounds that act via morphine receptors to produce morphine-like effects are called opoids. Special tests should be used for synthetic opioids, if available. Any positive result with opiate immunoassays must be further investigated to elucidate whether an illicit drug was used or whether antitussives were administered for a common cold. Many assays [1881,2109,2110] and several pharmacokinetic studies have been published.

The potent pain-killer bezitramide is abused by many drug addicts who know that it does not cross-react in normal immunoassays. Unfortunately, essentially only fairy old papers on this drug are available [684–686,2112]. The

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Amphetamine (dex)		12–30	3.2–5.6	0.05–0.15	0.2–1	75,336
Benzphetamine					14	75
Chlorphentermine		35–44	3	0.1		75
Cocaine		0.5–1.5	1.2–1.9	0.1–0.3	0.9–20	36,336
	Benzoylecgonine BZE	5–8				
	Ecgonine Methylester EME	3.5–6				
Diethylpropion = Amfepramone		1.5–2		0.007–0.2	>1	36,75
Fenfluramine		11–30	1000	0.03–0.3	>0.5	36,338
	Norfenfluramine	32				
Methamphetamine		12–34		0.01–0.2	0.2–5	75,336,338
	Amphetamine	12–30	3.2–5.6	0.05–0.15	0.2–1	
Methylphenidate		1–4	11–33	0.004–0.02	>0.5	36,75
	Ritanilic Acid			0.08–0.25		
Pemoline		11	0.2–0.6	0.7–6	>5	75
Phendimetrazine				0.02–0.09		75
Phenmetrazine		8		0.07–0.13	>0.5	75,338
Phentermine		19–24	3–4		>1	75

Table 2.11. *CNS Stimulants and anorectics*

same is more or less true for buprenorphine even though some recent data have been published [688–690,2024]. Codeine, dihydrocodeine, dextromethorphan and ethylmorphine have been studied [691–695,703–705,2113,2114]. Dextromoramide and d-propoxyphene can be assayed by GC-MS and/or HPLC [696–699,1786]. Dilaudid can be assayed by HPLC with EC detection [700] and dipipanone by capillary GC [701]. The endogenous opioid β-endorphin has recently been monitored by HPLC [702]. Etorphine can be assayed by GC-MS [706].

A long list of papers has been published on heroin and its metabolites monoacetylmorphine and morphine [167,707–713,727–738,1875,1902,2115]. It is sometimes difficult, but in principle it is possible to distinguish heroin from morphine abuse. Some analytical methods for the detection of hydromorphone [714–716], levorphanol [717] and meptazinol [718–719] are available. Methadone has been studied in various body fluids [720–725,2116] and hair [726]. Analytical methods for nalbuphine [740,741,2118,2119], the opiate antagonists levallorphan [2028], nalmefene [1985], naloxone [742] and naltrexone [1880], noscapine, an opium impurity [743], oxycodone [744–746,1839], pentazocine [747], meperidine or pethidine [748], phenoperidine [749], pholcodine [750,751, 1823], piritramide [752,753], tilidine [754–756] and zipeprol, a new antitussive agent [205,757,1845,2026] are also available.

Fentanyl derivatives. The diagnosis of poisonings related to these compounds is rather difficult, as very low amounts are usually involved. They can be detected only when especially dedicated methods are used. A selection of papers on alfentanil, fentanyl, p-fluorofentanyl, α-methylfentanyl, sufentanil etc. can be recommended [758–765,1889–1893]. Pharmacokinetic data are summarized in Table 2.12.

Designer drugs and hallucinogens (psychomimetics, psychodysleptics). In the media, there are many speculations on designer drugs. These drugs do exist on the illicit market, but are rarely encountered, although their use is seemingly increasing [603,766,1914–1916]. They include methoxyamphetamines, for instance DMA, DOB, DOM=STP, PMA and TMA, pethidine analogues like MPPP and phencyclidine, tryptamine analogues, like DET, DMT, DPT and etryptamine. MPPT, an impurity of MPPP, is of great toxicological concern [1907]. Fentanyl analogues must also be considered as designer drugs. Natural and semi-synthetic hallucinogens include cannabis, LSD, mescaline and psilocybin. Several papers have described the identification of several drugs and metabolites [767–769]. Methoxyamphetamines can be identified by LC-MS [796]. 4-bromo-2,5 dimethoxyphenethylamine (DOB) has been involved in acute poisonings [770–772]. Recent studies have been performed on methylenedioxyamphetamine (MDA) [780,789,1951]. Etryptamine has caused several deaths [773–775].

Entactogens. A new group of substances including MDMA and related compounds is called "entactogens" to distinguish the group from hallucinogenic amphetamines and central psychostimulating phenethylamines. These compounds like methylenedioxyethylamphetamine (MDEA = MDE = Eve) [781, 1774,1919], or the more popular methylenedioxymethamphetamine = MDMA = XTC = ecstasy were investigated [687,782–789,1915–1917,1951]. Impurities may give rise to

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Alfentanil		1.2	0.5–1	0.15–0.6	>0.2	36,75
Bezitramide				~0.005		687
Buprenorphine		2–6	2.5	0.0004–0.0006		36,75
	Norbuprenorphine					
Butorphanol		2.7	5	0.001–0.002		75
	Norbutorphanol					
Codeine		3–4	3.6	0.05–0.3	0.5	36,336
	Morphine	1–5	1.5–5	0.01–0.12	0.15–0.5	cf Morphine
	Norcodeine					
Dextromethorphan		2.5–3.9	1.1–6.4	0.001–0.008		36,75
	Nordextromethorphan	2.7–33		0.28–0.5		36
Dextromoramide				0.01–0.08	0.3–1	698
	Desalkyldextromoramide					
Dextropropoxyphene		8–24	12–16	0.1–0.75	>1	36,336
	Norpropoxyphene	24–34		0.1–1.5	2	
Dihydrocodeine		3–6	1.1–3.5	0.03–0.25	>1	36,338
	Dihydromorphine					
Dipipanone		3.5		0.03–0.08		36
Fentanyl		1–6	3–4	0.001–0.01	>0.1	36,75
	Norfentanyl					
Heroin = Diamorphine		1.7–5.3 min	25			75,727,730
	6-Monoacetylmorphine	9–40 min				
	Morphine	1–5	1.5–5	0.01–0.12	0.15–0.5	cf Morphine
Hydrocodone		3.8		0.001–0.002	0.2–0.6	75
Hydromorphone		1.5–3.8	1.2	0.02–0.03	0.02–1.2	75
Levorphanol		10–12	10–13	0.01	>1	36,75
Meptazinol		1.5–6	3.1	0.025–0.25		36,338

Table 2.12. *Opioids, antitussives and antagonists (continued overleaf)*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Methadone		6–8	5	0.1–0.75[a]	0.4–1	36,336,599
	Normethadol+EDDP+EMDP					75
(alpha)-Methylfentanyl					0.002–0.01	75
Morphine		1–5	1.5–5	0.01–0.12	0.15–0.5	36,75,337,733
Nalbuphin		2–8	3.7–3.9	0.04–0.06		36,75
Noscapine		2.5				45
Oxycodone		4–5		0.009–0.04	>0.2	45
Pentazocine		2–3	2.5–7.8	0.05–0.2	1–5	25,45,336
Pethidine = Meperidine		3–8	3.7–4.2	0.2–0.8	1–5	36
	Norpethidine				1–6	75
Phenazocine				0.005–0.008		36
Phenoperidine		3.2	5.7	>0.004		36
Pholcodine		32–43	30–49			36
Piritramide				0.01–0.05		752
Sufentanil		2–5	2.9	0.06 µg/l		1889
Tilidine		0.5–5	2.1	0.05–0.1	1.7	45,338,754
	Nortilidine			0.1–0.17	4.4	
Tramadol		7–9	3.3	0.1–1		45,338
Zipeprol				0.1	6.7	205
ANTAGONISTS						
Nalmefene				0.02–0.1		1985
Naloxone		1–1.5	2.8–5	0.01–0.03		36,75,338
Naltrexone		1.1–13	14–19	0.2		36

[a]Higher in maintenance therapy.

Table 2.12. *Opioids, antitussives and antagonists*

some concern [1932]. It is particularly difficult to make a distinction between the many possible isomers [790–795]. The street market obviously makes no distinction between these substances: they are all called "ecstasy", but sometimes tablets contain only caffeine, or caffeine and amphetamine, or a series of N-substituted 3,4-methylene-dioxyphenylbutamines like the one contained in tablets called "Fido Dido" [2121].

Phencyclidine. Phencyclidine or PCP is only rarely seen outside the US. Methods are available for screening by immunoassay [797–799,1787–1788] and for confirmation [1729]. The detection of impurities, like ethyl-1-phenylcyclohexylamine (PCE) has been published [800].

Cannabis. Apart from alcohol, cannabis is the widest substance of abuse under the names hashish or marihuana. A recent collection of papers was published on the determination of cannabinoids in body fluids [801]. Many recent methods of analysis in urine and plasma [224,802–806,1783,1883–1887,2122,2203], metabolism and pharmacokinetics [807–808,1809,1926], as well as the interpretation of results [72,809–812,2190] and interferences in GC/MS [1882] are available.

LSD. Lysergic Acid Diethylamide can cause death, normally not by pharmacological overdoses, but through other means such as trauma due to uncontrollable hallucinations. Analytical methods for body fluids are now available [776–779,2025].

Pharmacokinetic data are summarized in Table 2.13.

Ethanol. Ethanol is the most widely abused substance and this is apparently socially acceptable. Ethanol blood levels have been found to be higher in women than men [815]. A review on blood ethanol determination was recently published [813]. New methods, like NMR, have been discussed [1817]. There may be other alcohols, the so-called "congeners", which can be found in body fluids, when alcoholic drinks have been ingested [814,1600]. "Alcohol blockers" were critically reviewed [816]. Disulfiram may be determined by HPLC [817]. No analytical methods were found for acamprosate. The metabolism of difebarbamate, a drug used in the treatment of alcoholism, was studied [1983]. A long discussion, especially about measurement interferences, followed the introduction of intoxilyzers or breath alcohol analyzers [818]. Biological markers like carbohydrate-deficient transferrin in chronic alcohol abuse are of growing interest [819]. An unusual metabolite of ethanol, the ethyl-glucuronide, has been determined in the blood and urine [2123].

Smoking. Concern over smoking is steadily growing, as life insurance companies increasingly tend to offer differing conditions to smokers and to non-smokers or never-smokers. Several analytical methods have been proposed for the detection of nicotine and the metabolite cotinine in biological fluids [820–824,1984] as well as in hair [825]. Other tobacco alkaloids, like anabasine and anatabine, were detected in the urine of smokers and smokeless tobacco users [826]. Elimination pharmacokinetic studies to distinguish smokers from non-smokers [827] and sensitivity studies to nicotine were performed [828]. Pharmacokinetic data are summarized in Table 2.14.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Dimethyltryptamine		0.5		0.03–0.1		75
Etryptamine					5.6	775
LSD		3–4	0.3	0.001–0.005		75
MDA				<0.4	>1	75
MDEA					2	782
MDMA = XTC		7.6		0.1–0.35	0.5–1	75,337
Mescaline		6		2–15	>9	75
p-Methoxyamphetamine = PMA					0.4–1.8	75
Phencyclidine = PCP		7–46	5.3–7.5	0.004–0.007	0.1–0.8	75
THC		14–36	4–14	0.001–0.02		75,339,801
	8,11-Dihydroxy THC					
	11-Hydroxy THC					
	THC-COOH			0.002–0.25		1809,1886,1887

Table 2.13. *Hallucinogens and designer drugs*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Disulfiram		6–8.5	8.2	0.05–0.4	5	36
	Diethyldithiocarbamate DDC	10–20		0.3–1.4	6–17	75,336
Ethanol		2–14	0.5–0.6	0–25	1000–2000	75,337
	Acetaldehyde			0–30	100–125	336
Nicotine		1–4	1–2.6	0.01–0.1 (smoking)	>5	45,75
	Cotinine			0.001–0.3	0.3–1	336

***Table 2.14**. Miscellaneous addictive drugs and antagonists*

Anticonvulsants

A great number of methods are available as there is a need for therapeutic monitoring [829,2145]. Screening methods for acute poisonings have been described [830] and developments in the therapeutic monitoring of several drugs have been recently reported [831–835]. The pharmacokinetic optimization of old and new drugs [836] as well as the pharmacokinetics of new generation anticonvulsants [837] have been reviewed. Pharmacokinetic data are summarized in Table 2.15. Analytical methods and the pharmacokinetics of various antiepileptics have been reported, for example carbamazepine [838–840], clonazepam [841–844], ethosuximide [857], felbamate [845], lamotrigine [846–847], oxocarbamazepine [848], phenytoin [849], sulthiame [850], tiagabine [851], valproic acid [852–857], and vigabatrin [858,859].

General anesthetics

As these compounds are normally used only by anesthesiologists in hospitals only, they are not very often encountered in toxicology laboratories. However, iatrogenic accidents may occur and abuse has been reported. Analytical procedures [860,1824,2146] and pharmacokinetics were reviewed [861,862]. A sudden death following cyclopropane inhalation [863] as well as the recreational use of enflurane with a fatal issue were commented on [864]. The determination of embutramide in biological matrices was published [2124]. Etomidate pharmacokinetics [865] and also to the toxicology of nitrous oxide [867,868] were investigated. Several propofol poisonings [869–872] and ketamine poisonings were studied [873,2147]. The quantification of sevoflurane was published [874] as well as the determination of plasma inorganic fluoride [2125]. Many barbiturates, like hexobarbital [875], thiopental [876–878] and thiamylal [879, 880], have been studied. Pharmacokinetics are summarized in Table 2.16.

Local anesthetics

Local anesthetic agents are not frequently seen in toxicology laboratories, with the exception of lidocaine. Hattori et al. [881] investigated the determination of several local anesthetics in body fluids by GC with surface ionization detection. Bupivacaine and metabolites can be quantified by HPLC with enantiomeric separation [882,883,2126] or by GC [884]. A recent method for procaine determination has been reported [885]. Pharmacokinetic studies are summarized in Table 2.17.

Neuromuscular blocking agents and skeletal muscle relaxants

Drugs from these groups are often overlooked by toxicology laboratories, if no special precautions are taken, as they are not easy to detect and as several have very short elimination half-lives. An up to date pharmacokinetics review is available [886]. Recent analytical papers on alcuronium [887], atracurium [888, 1913], gallamine [889], mivacurium [890,2127], pancuronium [891], succinyl choline [892,1864–1867,1948] and vecuronium [893–895] can be recommended. Analytical methods have been published concerning baclofen [896,897], chlormezanone [898,899] and dantrolene [900]. Pharmacokinetic properties are summarized in Table 2.18 and 2.19.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Beclamide		2.5–3	55			36
Carbamazepine		30–40	0.8–2	4–10	12–70	36,337
Clonazepam		18–45	2–4	0.03–0.08	>0.08	36
	7-Aminoclonazepam					
Dimethadione		600		500–1000	>1000	45,337
Ethosuximide		53–56	0.7	40–100	150	45,337
Felbamate		14–22	0.7–0.8	23–32		837
Gabapentin		5–7	0.7	2–3		837
Lamotrigine		18–30	1.1–1.3	1.3–1.9		837
Mephenytoin		12–32		20–40		75
Mesuximide		0.7–2.6		0.04–0.08		75
	N-Desmethylmesuximide	28–57		10–30	40	75
Oxocarbamazepine		1–6	3.3–17.7	0.4		848
	Monohydrate Derivative (MHD)	5–14		5		
Phenobarbital		48–144	0.5–0.6	20–40	60–80	75,337
Phensuximide		5–12		4–20		75
	Norphensuximide			1.4–2.1		75
Phenytoin		7–60	0.5–0.7	8–18	>20	36
Primidone		4–22	0.6	5–12	15	75,337
	Phenobarbital	48–144	0.5–0.6	20–40	60–80	75,337
	Phenylethylmalonamide (PEMA)	13–19	0.6–0.8			
Remacemide		3.1–5.1		0.4–1		837
Stiripentol		13		0.4–4.2		837
Sulthiam		3–30		1–12		336,338
Tiagabine		4.5–13.4		0.04–0.6		837
Topiramate		9–23		1.7–28		837
Trimethadion				20–40		336
	Dimethadion			500–1000	>1000	336
Valproic Acid		9–21	0.1–0.4	50–100	150	40,336
Vigabatrin		(S)6–(R)8	0.65–1.05	10–60		36,837

***Table 2.15**. Anticonvulsants*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Enflurane		36	8.6	50–100		75,339
Ether				anaesth. 20–180	>600	75
	Ethanol + Acetaldehyde					
Etomidate		2–11	2–4.5	0.3–0.5		36
Halothane		2 min–2 h	1	anaesth. >50	>60	36,75,339
Ketamine		2–13	3–4	0.1–1		75,339
Methohexital		1–3	1–2.6	5		339
Methoxyflurane				125–200		339
Nitrous Oxide (N_2O)				anaesth. 20–200	>80	36,75
Pentobarbital		20–30	0.5–1	1–4	12–50	75,338
Propofol		0.5–1	5	1–10		36,337,339
Thiamylal					120	880
Thiopental		6–46	0.7–2.3	1–5	>10	36,338
	Pentobarbital	20–30	0.5–1	1–4 (25–40)*	12–50	36,75

*In traumatic patients.

Table 2.16. *General anaesthetics*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Amethocaine		short		local		36
Bupivacaine		1–3	0.5–2.7	1–4	4–8	36,337
Lidocaine = Lignocaine		0.7–1.8	1.4–2.2	0.4–5.0	>8	40,75,337
	MEGX			0.07–0.2		75,337
Mepivacaine		2–3	~1	2–4	6	25,337
Prilocaine		1–2		1–5	13	25,75
Procaine		0.1	0.3–0.8	2–15	20–40	25,75,336

***Table 2.17**. Local anaesthetics*

Compound Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Alcuronium Chloride		3.3–36	0.2–0.4	0.8–2.21		886
Atracurium Besilate		17–20 min	0.16			36
Doxacurium Chloride		1.5–4				886
Gallamine Triethiodide		2–4	0.1–0.2	1–10		36,339
Metocurine = Dimethyl-tubocurarine		4–6	0.3	0.14–0.2		886
Pancuronium Bomide		1.9–3.1	0.2–0.4	0.2–0.5	1.6	36,339
Pipecuronium Bromide		1.7–4.4				886
Suxamethonium Chloride = Succinylcholine		2–10 min			2–3	1778
d-Tubocurarine Chloride		2.5–6.2	0.3–0.6	0.2–0.7		36,886
Vecuronium Bromide		0.1–2.5	0.2–0.3	0.2–0.4		36,339,1778

Table 2.18. *Neuromuscular blocking agents*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Baclofen		3–4	0.8–0.9	0.08–0.4		339
Chlormezanone		20		2.5–3.5	50	75,338
Chlorzoxazone		1.1		9–40		25
Cyclobenzaprine		1–3d		0.003–0.03	0.4–0.5	75
Dantrolene		4–22	1.2	0.3–1.4		36,337
	5-Hydroxydantrolene					
Tetrazepam		10–26	0.8–1.6	0.05–0.7		338,340
	Nortetrazepam	30–42				340

Table 2.19. *Skeletal muscle relaxants*

Antiparkinsonian drugs

Most of these drugs are found at very low concentrations in the blood and are therefore difficult to identify and quantify [901]. Assays have been proposed for apomorphine [902,903], benztropine [904], bromocriptine [905], and carbidopa and levodopa [906]. Mena et al. [907] studied the pharmacokinetics of levodopa. Immunoassays for ergotamine and dihydroergotamine were studied [908]. A HPLC method for α-methyldopa in man was proposed [909].

Selegiline is a very challenging compound as it gives rise to amphetamine and methamphetamine which are the R (–) enantiomers of the psychoactive S (+) enantiomers found in drug abuse. A chiral separation is required to distinguish between selegiline metabolites and stimulating amphetamines [664,666, 910,911,1775]. A HPLC method for terguride was proposed [2128]. Pharmacokinetic data are summarized in Table 2.20.

Drugs affecting the autonomic nervous system

Sympathomimetics. Many of these drugs are very polar and circulate in blood at low concentrations. Multi-methods are available, such as for catecholamines like epinephrine, norepinephrine, dopamine and L-dopa [912,913,915] and other α-agonists [914]. Several methods are available, but they are essentially dedicated to one major substance and its metabolites, for instance clenbuterol [916–918,1825,2148], dopexamine [919], ephedrine [920], epinephrine [921–922], norephedrine [923,924], phenylephrine [925], ritodrine [926], salbutamol [927–929,1831] and terbutaline [930]. Pharmacokinetic data are summarized in Table 2.21.

Sympatholytics. Ergotamine can be monitored by various techniques [931, 932] and phentolamine by HPLC [933]. Yohimbine was recently investigated [934–936]. Pharmacokinetic data are summarized in Table 2.22.

Parasympathomimetics. As for any other drugs of the autonomic nervous system, these are difficult to analyze. Ion-pair HPLC has been proposed for pyridostigmine, neostigmine and edrophonium [937], GC and GC-MS for quaternary ammonium compounds [938,939]. The clinical pharmacokinetics of a selection of cholinesterase inhibitors was studied [940]. HPLC methods have been proposed for physostigmine [941], pilocarpine [942] and pyridostigmine [943]. Pharmacokinetic data are summarized in Tables 2.23 and 2.24.

Parasympatholytics. Various assays for atropine have been proposed [944–947]. Biperiden was monitored in the plasma of volunteers [948,949]. N-butylscopolamine and homatropine can be monitored by membrane electrodes [950], acetylcholine and choline in blood by HPLC [951]. Methods have recently been described for ciclotropium [952], clidinium bromide in capsules [953], orphenadrine [954], oxitropium [955], oxybutynine [956,957], pirenzepine [958], procyclidine [959], propantheline [960], trihexyphenidyl [961,962] and vamicamide [1799]. Pharmacokinetics are summarized in Table 2.25.

Spasmolytics. Only very few papers are available. A method for the detec-

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Amantadine		12	0.2	0.2–0.9	>1	339
Apomorphine		0.5	2			36
Bromocriptine		3–15	1–3.7	0.001		36
Carbidopa		2–3		0.2–0.4		36
Levodopa		1.3	0.4–12.7	0.2–0.4		339,901
	Dopamine	6–12 min	0.9	0.01–0.1		36,339
	Noradrenaline	0.6–3 min	0.09–0.4	0.2–2 pg/l		36
Pergolide		15–42	17–32	0.0001–0.001		36
Selegiline		16–69	4.7	0.03–0.05		36
	Norselegiline R(–)-Methamphetamine R(–)-Amphetamine					

Table 2.20. *Antiparkinsonian agents*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Adrenaline = Epinephrine		0.1		30–160 ng/l		36
Clenbuterol		30	4	50–90 ng/l		34
Dobutamine		2.4 min	0.2	0.02		36,339
Dopamine		6–12 min	0.9	0.01–0.1		36,339
Dopexamine		7 min	0.45	0.1		36
Ephedrine		3–11	1.7–4.5	0.02–0.1	1	36,337,338
	Norephedrine	3–7	2.8–4.5	0.06–0.2	>40	36
Etilephrine		3	2.3			339
Fenoterol		6–7		0.003–0.004		36
Isoprenaline = Isoproterenol		>2.5	0.5	0.0004		36,75
Norepinephrine=Noradrenaline		0.6–3 min	0.09–0.4	0.2–2 pg/l		36
Orciprenaline = Metaproterenol		2–20	7.6			36,339
Oxymetazolidine		5–8d				36
Phenylephrine		2–3	4.8–5	0.004–0.07		36
Phenylpropanolamine = d,l Norephedrine		3–7	2.8–4.5	0.06–0.2	>40	36,75
Propylhexedrine				0.01	>0.3	75,339
Pseudoephedrine		5.4–8	2–3	0.4–0.6	>10	36,75
Rimiterol		<5 min		0.002–0.009		36
Ritodrine		15–20	0.6–0.9	0.015–0.030		36
Salbutamol		2.7–5	2.8–4	0.004–0.016	0.01–0.06	36,1831
Terbutaline		14–18	1.6	0.001–0.03	>0.04	36,75
Xamoterol		16	0.64	0.04–0.15		36

Table 2.21. *Sympathomimetics*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Ergometrine		0.5	0.3–0.7	0.0005–0.001		36
	Desmethylergometrine					36
Indoramine		2–10	5.4–10.6	0.004–0.09		36
Phentolamine		1.5		0.005–0.01		36
Tolazoline		1.5–2		0.2–0.5		36
Yohimbine		0.2–1.1	0.3–3.9	0.04–0.06		934

Table 2.22. *Sympatholytics*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
4-Aminopyridine				0.025–0.075	0.15–0.2	337
Edrophonium Chloride		1.8	1.1	<0.15		339
Neostigmine		0.4–1.3	0.1–1.1	0.001–0.01		36
Physostigmine		0.2–0.4	0.2–1.07	<0.003		36
Pyridostigmine		0.4–1.9	0.5–1.8	0.04–0.06		36

Table 2.23. *Parasympathomimetics–cholinesterase inhibitors*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Obidoxime Chloride		1.1–1.5	0.17	1–26		36
Pralidoxime		1.2	0.6	<4		36

Table 2.24. *Cholinesterase reactivators*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Atropine		2–5	1–6	0.03–0.2	>0.2	36,339
Benzatropine				0.005–0.1	0.7	75
Benzhexol = Trihexyphenidyl		3–7		0.04–0.12		901
Biperiden		18	40–60	0.004–0.1		36,336
Dicyclomine = Dicyloverine		1.8–6	3.6	0.02–0.08	0.2	34,36,75
Hyoscine Butylbromide = Butyl-scopolaminium Bromide		4–8				36,1778
Ipratropium Bromide		1.6–4				1778
Orphenadrine		13.7–16.1	4.3–7.8	0.2–0.5	>1	36,75,339
	Desmethylorphenadrine			tot 0.05–0.2	tot 0.5–1	336
Oxibutynin		0.8–2.9		0.007–0.02		36
Oxitropium Bromide		2.4	3.6	~0.002		955
Pirenzepine		11	14	0.2–0.3		36
Procyclidine		12.6	1	0.08–0.1	>0.4	75,901
Propantheline Bromide		1.8–3		0.02		25
Scopolamine = Hyoscine		3–8	1.4	0.0001–0.001		339

Table 2.25. *Parasympatholytics–anticholinergic/antimuscarinic agents*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Dihydroergotamine		1–15	5.6–30	0.002–0.003		36,339
Ergotamine		2	1.8			36
Lisuride		~8	2.3–2.4			36
Methysergide		0.75				339
Pizotifen		26	6.4–7.4	0.007–0.009		36
Sumatriptan		2	2.4	0.001–0.03		36,45,966
	Indole acetic acid analogue					

Table 2.26. *Antimigraine agents*

tion of camylofin [963] and a sensitive HPLC method for mebeverine were described [964].

Antimigraine drugs. A GC-MS method for ergotamine has been investigated [965]. The drug sumatriptan was investigated both from the analytical [966] and pharmacokinetic viewpoint [967]. Pharmacokinetic data are summarized in Table 2.26.

Minor analgesics, anti-inflammatory drugs and drugs used in gout

Minor analgesics and non steroidal anti-inflammatory drugs

These are frequently seen (if not detected, when not especially suspected!) in most toxicology laboratories, both for acute and chronic poisonings. Screening methods are available, including GC, GC-MS, TLC and HPLC [968–977,1822]. Orme et al. [978] discussed plasma concentrations and therapeutic effects. Methods for the analysis of amfenac sodium [979], antipyrine [1801], and diclofenac sodium and metabolites [983–986], were studied. The pharmacokinetics of gold complexes [980,981], benoxaprofen [982] and flurbiprofen enantiomers [991] were discussed. Diflunisal-related fatality and pharmacokinetics were reported [987,988]. The metabolism of etodolac was considered [989] and a HPLC method discussed [990]. Glafenine and floctafenine can be assayed by HPLC [992]. Several methods including the separation of stereoisomers are available for ibuprofen [993–996]. Pharmacokinetic studies [997] and an improved HPLC method [998] are available for indomethacin. A metabolic study of isoxicam in man was performed [999]. A HPLC method for ketoprofen and naproxen in plasma and urine was reported [1000]. A method for ketorolac was investigated [2149]. Other methods including pharmacokinetic studies were published [1001–1005].

Lornoxicam and metabolites were monitored using HPLC [1006]. Pharmacokinetic studies of meclofenamate sodium were published [1007]. HPLC was used to monitor mefenamic acid [1008]. Morazone was determined in rat plasma and urine by GC [1009], and gold concentrations in patients treated with myocrisin [1010]. Nabutemone was determined by HPLC with fluorimetric detection [1011], whereas pharmacokinetics of urine compounds were investigated [1012]. Andersen et al. [1013] reported the simultaneous determination of naproxen and metabolites by HPLC. Chang et al. [1014] determined nefopam by GC using an NP-detector. Niflumic acid can be quantified by HPLC in plasma [1015]. Edinboro et al. [1016] compared paracetamol determinations by different methods. Piroxicam was monitored by several authors [1017–1019]. Propyphenazone was monitored in plasma using HPLC [1020]. Analytical and pharmacokinetic studies of salicylates are available [1021–1023,2053], including salsalate [1024]. A radioimmunoassay for the determination of substance P [1025], HPLC methods for tiaprofenic acid [1026], tolmetin [1027] and pharmacokinetic studies of tolfenamic acid [1028–1030], have been discussed. The veterinary analgesic xylazine may also be used by man and can be quantified [1031–1034]. Pharmacokinetic data are summarized in Table 2.27.

Drugs used in gout

Brown et al. [1035] determined allopurinol and the metabolite oxypurinol. A HPLC method for colchicine has been discussed [1036]. Veenendaal et al. [1037] reported a HPLC method for probenecid determination. The pharmacokinetics of probenecid were investigated [1038] and one death reported [1039]. Sulphinpyrazone and metabolites can be detected and quantified by HPLC [1040,1041]. Pharmacokinetic data are summarized in Table 2.28.

Antihistamines

The chromatography of histamine H_1 blockers including screening methods was recently reviewed [1042]. Other screening procedures [1043,1044] and the pharmacokinetics of several antihistamines [1045] were studied. Astemizole and metabolites can be determined by HPLC [1046]. One case of overdose in children was reported [1047]. The separation of brompheniramine enantiomers using cyclodextrin in the mobile phase was performed [1048]. The bioavailability of cetirizine [2129] and the urinary metabolism of chlorphenoxamine were investigated [1049]. One case of cyclizine overdose was reported [1050]. Dimethindene was quantified in plasma [1800]. Diphenhydramine and doxylamine can be monitored by several methods [1051,1052]. Even histamine can be quantified by HPLC, using fluorimetric detection [1053]. The determination and pharmacokinetics of loratidine were investigated in patients with renal insufficiency [1054,2130]. The determination of mequitazine [1055], the separation of terfenadine enantiomers and metabolites [1056–1058,2031] and the metabolism of tripelennamine in man [1059] were investigated. Pharmacokinetic data are summarized in Table 2.29.

RESPIRATORY SYSTEM DRUGS

Drugs used in asthma

Antiallergic drugs. Ketotifen can be monitored by negative ion CI-mass spectrometry [1060] and its pharmacokinetics was studied by Grahnen [1061]. Nedocromil sodium was determined in plasma and urine using a radioimmunoassay [1062]. Oxatomide can be monitored after solid-phase extraction [1063] and a radioimmunoassay for sodium cromoglycate was proposed [1064]. Pharmacokinetic data are summarized in Table 2.30.

Xanthines. Caffeine and its metabolites can be detected by HPLC [1065]. Overdoses have been reported [1066,1067]. Attention must be paid to theophylline immunoassays which can give false positives due to cross-reactivity [1068]. Dyphylline, diprophylline and doxofylline can be monitored by HPLC [1069]. The pharmacokinetics of dyphylline were studied [1070]. A selection of methods and poisoning case reports involving theophylline is recommended [1071–

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma(serum) conc. (mg/l) Therap. range	 Toxic range	
Acetyl Salicylic Acid		15–20 min	0.2			36
	Salicylic Acid	3–20	0.1	30–300	400–500	75,336
Auronofin		5–25d	0.05–0.1	0.06–0.7(Au)		36,45,75
Aurothiomalate		250d	0.1	0.7–3 (Au)		36
Benoxaprofen (withdrawn)		30–35		4–50		36,45,339
Diclofenac		1–2	0.12	0.05–2.5		45,336
	4-Hydroxydiclofenac					
Diflunisal		8–12	0.1	40–90		36,45,339
Etodolac		6–7.5	6.5–7	>60		36,45
Fenbufen		10–17	3	20–60		36,45,339
	4-Biphenyl Acetic Acid (BPAA)					
Fenoprofen		1.5–3	0.1	20–30		36,75
Flurbiprofen		2–6	0.1			36,339,991
Ibuprofen		2	0.1	0.5–50	>80	75,339
Indomethacin		1–16	1	0.8–2.5	4–6	36,336
Ketoprofen		1–3	0.1–6	1–5		36,75
Ketorolac		4.4–5.6	0.1–0.3	0.8–2.7		36
Mefenamic Acid		3–4	1.3	15–30	100	36,338
Metamizol		3.3–8		0.05–1	2	338,339
Nabumetone						36
	6-Methoxy-2-naphthyl Acetic Acid = 6-MNA	27.5–34.5	7.5	52–67		
Naproxen		12–15	0.9	50–200	>200	36,75,336
Nefopam		3–11	10	0.03–0.05	>4	36,338
Niflumic Acid		2–3		2–35		338
Oxyphenbutazone		50–70	0.14	20–50		339
Paracetamol		1–3	0.8–1	10–20	100–150	36,336
Phenacetine		0.6–1.3	1–2	5–20	50,336	

Phenazone		7–12	0.5–0.6	5–25	50–100	45,75,337
	3-Hydroxymethylphenazone 4-Hydroxyphenazone Norphenazone					
Phenylbutazone		49–142	0.1–0.2	50–150	250–500	34,36,339
	Oxyphenbutazone	50–70	0.14	20–50		45,336
Piroxicam		30–60	0.1–0.3	2–20		36,75
Propyphenazone		<12	1.3			339
Salicylamide		0.25–1		5–40		75,338
Sulindac		7–16	2	0.5–5	>100	45,337
	Sulindac Sulphide	16–18		1–4		36,337
Tenoxicam		70		10–15		339
Tiaprofenic Acid		1.5–2		20–35		36
Tolmetin		5.5–8.5	0.1	30		36
Zomepirac (withdrawn)		4–10	0.6–1	1–4	>100	75,339

***Table 2.27**. Minor analgesics and NSAIDs*

Compounds	**Main metabolites**	**Elimination half-time**	**V_D**	**Plasma (serum) conc. (mg/l)**		**Ref.**
Parent drug		**(h)**	**(l/kg)**	**Therap. range**	**Toxic range**	
Allopurinol		0.5–40	0.6	1–10		337,339
	Oxypurinol	10–40		5–20		338
Benzbromarone		3–12	0.3	<2.5		339
Colchicine		0.1–20	1–10	0.003–0.03	0.02–0.25	36,75,339
Probenecid		4–17	0.1–11	40–200		36,339
Sulphinpyrazone		4–18	0.06–0.7	6–9		36

***Table 2.28**. Drugs used in gout*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Astemizole		20–30	48	0.0001–0.05		36,338,339
	Desmethylastemizole					
Azatadine		8.7	0.9			36
Azelastine		30–40				339
Cetirizine		6.6–10.9	0.5–0.6	0.2–0.6		36
Cyclizine		7–24		0.1–0.25		75,336
	Norcyclizine					
Cyproheptadine				0.03		36
	Norcyproheptadine					
Dexchlorophenamine = Dexchlorpheniramine		15–30	1–10	0.008–0.0116	>1	36,75
Dexbrompheniramine = Dexbromiramide		15–22	2.5–10	0.008–0.016		
Dimetindene		5–7				1778
Diphenhydramine		2.4–8	3.3	0.025–0.1	0.2–2	36,336
	Desmethyldiphenhydramine					
Doxylamine		10		0.07–0.14	1.2	1052
	Nordoxylamine				0.5	
Flunarizine		10–50d	43–78	0.03–0.1		339
Loratidine		7–19				36
	Descarboethoxyloratidine	11–24				36
Mebhydrolin		5.5				36
Mequitazine		18–40	57			36,1778
Pheniramine		16–19	3.3	0.1–0.3	>1	36,75
Terfenadine		16–23		0.001–0.005		36
Tripelennamine		2.9–5.3	9–12	0.1–0.2	>10	75
Tripolidine		1–5–4.5	0.9–16.5	0.001–0.01		36

Table 2.29. *Antihistamines*

Compounds Parent drug	Main metabolites	Elimation half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	Toxic range	Ref.
Cromoglycic Acid		1–1.5	0.3	0.0004–0.07		36
Ketotifen		7–27		0.7–1.5		36
	Norketotifen					36
Nedocromil Sodium		1.5–24 *	0.8	0.012–0.025		1778
Oxatomide		14		0.1		339

*Depends on the route of administration.

Table 2.30. *Antiallergic drugs used in asthma*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	Toxic range	Ref.
Caffeine		1.9–12.2	0.4–0.6	2–10	>15	36,75,338
	Theobromine 20%					
	Theophylline 8%					
	Paraxanthine 72%					
Doxapram		6–9	1.5	3–5		75
Dyphylline = Diprophylline		1.7–2.7	0.6–1.1	12–14	>40	36,75
Enprophylline		2.5	0.6			339
Theobromine		7.1–12	0.7	1–10		1075
Theophylline		1.4–12.8	0.5	5–20	>40	36,75

Table 2.31. *Xanthines and respiratory stimulants*

1074]. Theobromine can be monitored [1074], and pharmacokinetics were studied [1075].

Respiratory stimulants. Only a few methods are available. Baune et al. [1076] described the determination of almitrine. A GC-method was studied for doxapram [1077]. The metabolism of doxapram in human tissue cultures was studied [1078]. Pharmacokinetic data are summarized in Table 2.31.

CARDIOVASCULAR DRUGS

Cardiac stimulants and other inotropic agents

The chromatography of cardiac glycosides [1079] and the pharmacokinetics of newer inotropic agents [1080] were reviewed. Extensive experience in therapeutic drug monitoring, especially for digoxin, is available, including immunoassays [1081–1087] and HPLC [1079]. Cross-reacting interferences in immunoassay have been outlined [1088–1090], including Fab treatment [1955]. The plasma concentrations of enoximone were monitored in cardiac patients [1093]. The pharmacokinetics of β-methyldigoxin [1091] and a HPLC method for milrinone [1092] were discussed. Pharmacokinetic data are summarized in Table 2.32.

Antiarrhythmics

A general method for the detection of antiarrhythmic drugs and metabolites was proposed [1094]. The performance of 3 immunoassays for N-acetyl-procainamide was compared [1095]. Ajmaline can be monitored by HPLC [1096] and a fatal ajmaline poisoning in children was reported [1097]. Amiodarone and metabolites can be monitored after solid phase extraction membrane [1098]. A GC-MS method for the identification of detajmium and metabolites in body fluids [1852], a HPLC method for the determination of disopyramide and metabolites [1099], the steady-state pharmacokinetics of disopyramide in children [1100], and the metabolism and pharmacokinetics of encainide [1101, 1102] were studied. A HPLC method for ethmozine (moricizine, moracizine) in plasma [1103] and various methods for the determination of flecainide after acute poisonings [1104–1107] have been published. Lignocaine (lidocaine) can be monitored by immunoassays or HPLC and the metabolite monoethylglycinexylidide and glycinexylidide can be separated [1108–1110]. Lorajmaline and its metabolite ajmaline were monitored in body fluids using HPLC [1111]. A HPLC method for the quantification of mexiletine and metabolites [1112], and the pharmacokinetics of prajmaline [1113] have been described. Various HPLC methods [1114,1115] and pharmacokinetic studies [1116,1941] have been published for propafenone. A method for the HPLC determination of quinidine and selected metabolites [1117], stereoselective pharmacokinetic studies of tocainide in uremic patients and in healthy subjects [1118] were performed. Pharmacokinetic data are summarized in Table 2.33.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Acetyldigitoxin		43–53	4.2	0.001–0.0015		339
Amrinone		2–5	1.3		>2.5	339,1778
Digitoxin		3–16 d	0.5–40	0.01–0.03	0.04–0.18	36,75
Digoxin		20–50	6	0.0008–0.002	0.002–0.02	36,337
Enoximone		1.2–4	2.5			339,1778
Lanatoside C		21–43	4.4	0.001–0.0015		339
Medigoxin=Beta Methyldigoxin		40	13	0.0005–0.002		339
Milrinone		0.8–2.4	0.3	0.08–0.4		36
Ouabain		18–25	10–15	0.0002		34

Table 2.32. *Cardiac stimulants/inotropic agents*

Compounds Parent drug	Main metabolites	Elim. half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Ajmaline		0.1–5.5	2			339
Amiodarone		2–25d	62–66			75
	Desethylamiodarone			tot 2–5	tot 5–8	336
Aprindine		20–27	8	0.75–2.5	2	45,336
Bepridil		33		0.6–2.5		339
Disopyramide		4–10	0.7	2.5–7	20	36,45,338
	Nordisopyramide	4–13			8–10	
Encainide		1–3	3.8	0.02–0.06		36
	ODE=O-Desmethylencainide	3–11		0.08–0.2		
	MODE=3-Methoxy-O-Desmethylencainide	6–12		0.09–0.25		
Flecainide		14–20	9–10	0.2–1	1–1.5	36,339
	2-O-Desalkylflecainide					
Lidocaine		1.6	1.3	0.4–5	>8	36,336
	MEGX			0.07–0.2		75
Lorajmine						
	Ajmaline	0.1–5.5	2			339
Lorcainide		3–15	~8	0.05–0.5		
	Norlorcainide	20–40		0.16–0.68		
Mexiletine		10–17	5.5–9	0.5–2	1.5–3	36,45,337
Moracizine = Moricizine = Etmozine		1–9	8.3–11.1	0.045–0.15		36
Prajmaline		6		0.05–0.15		339
Procainamide		2.5–5	2	4–10	>15	45,336,339
	N-Acetylprocainamide	6–9		tot 10–30	tot 40	
Propafenone		2.4–10	3.6–4.4	0.2–1.6	1.1–7.7	36,336,339,2002
	Norpropafenone			0.07–0.7		
Quinidine		4–12	2–3	2.5–5	6–10	36,45,336
d-Sotalol		7–18	1–2	0.8–5	>2	36,45,337,1826
Tocainide		8.9–40.6	1.4–3.2	4–10	25	36,336

Table 2.33. *Antiarrhythmics*

β-Blockers

Several general screening methods for the determination of β-blockers in body fluids have been reported [1119–1121,1826,2132,2150], including chiral separations [1122] and detection in hair [1123]. A review has been made by Davies [1120].

The pharmacology and analytical toxicology of acebutolol were studied [1124,1125,1833]. Atenolol can be monitored by HPLC [1126]. The pharmacology of bisoprodol and carvedilol have been studied [1127,1128]. The analytical toxicology and pharmacokinetic studies of metoprolol [1129,1130] and bunolol [2111], methods for the detection of nadolol [1131,2151], pindolol [1132] and enantiomeric separations for propranolol [1133,2152] and timolol [1134], have been discussed. Pharmacokinetic data are summarized in Table 2.34.

Calcium antagonists

The chromatography [1135], pharmacokinetics [1136,2133] and toxicology [1937,1950] of calcium antagonists have been reviewed.

The clinical pharmacokinetics of amlodipine [1137], a method for the determination and pharmacokinetics of bepridil [1860], a method using negative-ion GC-MS for the determination of benidipine [1138], pharmacokinetic studies of clentiazem [1139] have been published. Diltiazem and metabolites can be determined in body fluids by several methods [1140–1143]. The pharmacology and toxicology of dialthiazem have been discussed [1144,1145]. Pharmacokinetic studies of diperdipine in the dog [1977], several analytical methods for felodipine in plasma [1146–1148], a GC-MS method for the determination of fendiline [1149], a chiral HPLC method for gallopamil [1150], and the analytical toxicology and clinical pharmacokinetic studies of isradipine [1151–1153] have been reported. HPLC and GC methods [1154,1155] as well as several cases of nifedipine overdose [1156,1938] have been published. The pharmacokinetics of nimodipine [1157] and nisoldipine [1158] have been reviewed as well as the analysis and pharmacokinetics of nitrendipine [1159,1160]. Julien-Larose et al. (1161) reported the use of particle beam HPLC-MS for the structure elucidation of oxodipine and three metabolites. Several methods for verapamil enantiomers are available [1150,1162,1163] and pharmacokinetics have also been reviewed [1164,1165]. Pharmacokinetic data are summarized in Table 2.35.

Antihypertensive drugs

Only very few substances of this group can be included in the "general unknown" procedure for detection. As a consequence, they will be missed, unless special techniques are used.

Bretylium has been quantified by GC [1166] or HPLC [1167], and pharmacokinetics were reviewed [1168]. A special GC-MS method for clonidine, which

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Acebutolol		3–9	1–3	0.5–1.8	15–20	45,336,338
	Diacetolol	8–14		2–2.8		36
Alprenolol		2–3	3–3.4	0.05–0.1	>0.1	75,336,338
	Hydroxyalprenolol			0.04–0.06		336
				tot 0.1–0.2	tot 0.25–0.3	
Atenolol		6–7	0.5–1.5	0.2–0.6	2	36
Betaxolol		16–20	5.5–6.5			36
Bisoprolol		13.2	3	0.04–0.06		45
Carazolol		9		<0.015		338
Carteolol		5–6	4.05	0.05		45
Carvedilol		4–8	2	0.02–0.3		1128
Labetolol		5–8	3.4–10.7	0.025–0.2	0.5–1	36,45
Metoprolol		3–4*/ 7**		0.05–0.6	1	45,336
Nadolol		12–24	2	0.025–0.275		34,36
Oxprenolol		1–4.6	1.3	0.1–1	2–3	36,45,336
Penbutolol		22–27	10.4	0.3–0.7		45,336,339
Pindolol		3–4	1.2–2	0.01–0.07		36,337
Practolol		10–13	1.6	1–1.4		36
Propranolol		3–6	2.3–5.5	0.05–0.3	1–2	36,336
d,l-Sotalol		7–18	1–2	0.8–5	>2	36,45,336,1826
Timolol		2–5	1.7–3.6	0.005–0.1		36,336

*Fast hydroxylators.
**Poor hydroxylators.

Table 2.34. *Beta-blockers*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Amlodipine		30–60	15–25	0.001–0.03		36,339
Bepridil		33	8	0.6–2.5		339,1860
Diltiazem		2–11	5	0.05–0.3	0.8	36,337
	N-Desmethyldiltiazem					
Felodipine		12–36	10	0.002–0.01		36
Gallopamil		3–8				
Isradipine		1–16	2.83–4	0.01–0.06		36
Nicardipine		0.5–12	1.7			36
Nifedipine		2–6	0.3–1.2	0.04–0.160	>0.130	36
Nimodipine		1.1–5.7	0.9–2.3	0.01–0.03		36
Nitrendipine		6–11	6.6	0.01–0.06		339
Pinacidil		2.1–2.5	1.1	>0.05		339
Verapamil		2–10	4–7	0.03–0.75	>1	36,75
	Norverapamil			0.15–0.4	1	336

Table 2.35. *Calcium antagonists*

circulates at low levels and therefore needs special precautions to avoid losses and contaminations during the process, was described [1169,1856]. Daumas et al. [1170] proposed a GC-MS method for debrisoquine. A method for diazoxide [1171] and a HPLC method for hydralazine and metabolites [1172], have been published. Indapamide can be quantified in blood by HPLC [1173]. A metabolic study of indoramine [1174] and two HPLC methods for ketanserin [1175,1176] have been reported. Minoxidil can be monitored by HPLC [1177] and moxonidine by negative ion GC-MS [1178]. Pharmacokinetic interactions of moxonidine with digoxin have been described [1208] and the absolute bioavailability was studied [1986]. An electrochemical method for todralazine determination was published [1179]. A fully automated method for the new potassium channel opener UR-8225 in plasma was proposed [2134]. Pharmacokinetic data are summarized in Table 2.36.

Angiotensin converting enzyme (ACE) inhibitors

Many analytical methods have been developed to deal with the angiotensin peptides [1180]. Pharmacokinetic studies were performed [1181,1968]. Future perspectives have been reviewed [1967]. Sioufi et al. [1182] proposed a GC-MS method for benazepril and the metabolite benazeprilate. Captopril can be quantified by SIM-GC-MS [1183,1973] or HPLC [1184,1974]. Its psychotropic effects were studied [1185] and one overdose reported [1972]. Pharmacokinetic studies on cilazapril [1186,1966,1969,1970] and enalapril [1187], have been published. A radio-immunoassay for the active drug from the prodrug fosinopril was investigated in human serum [1975]. Imidapril and its active metabolite can be assayed by HPLC using fluorimetric detection [1190] or GC-MS [1976]. Lisinopril and enaprilate (a metabolite of enalapril) can be determined by radio-immunoassay [1188]. Chiou et al. [1189] described an HPLC-method for losartan. Pharmacokinetic studies of perindopril have been performed [1191,1993]. Several analytical methods and pharmacokinetic studies of quinapril are available [1192–1195]. Pharmacokinetic data are summarized in Table 2.37.

Cerebral, coronary and peripheral vasodilators

A NPD-GC method for bencyclane [1196] and a fatal poisoning [1197] were reported. Several methods for buflomedil [1198,1199,1853] and pharmacokinetic studies [1200,1201] are available. A RIA method for dihydroergotoxine was described [1202]. Kirch et al. [1203] performed a pharmacokinetic study of nifedipine-codergocrine combination. Several methods for dipyramidole [1204–1206], a negative-ion GC-MS method for heptaminol [1207], HPLC methods for nefiracetam and metabolites [1209], nicorandil [1992] and dimiracetam [2136] were published. The pharmacokinetics of oxiracetam were studied [1990]. Ethaverine and papaverine can be assayed by ion-selective electrodes [1210]. Several pharmacokinetic studies of pentoxipylline [1211,1212], and analytical

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Bethanidine		2–6		0.02–0.5		25
Bretylium Tosylate		4–17	3.4–8.2	0.4–2.4		36,45,339
Clonidine		8–25	0.3–4	<0.0005	0.02–	28,75
Debrisoquine		10–26		0.015–0.18		25,36
	4-Hydroxydebrisoquine	10				25
Diazoxide		2–36	0.2–0.3	15–50	>100	36,339
	Hydroxymethyldiazoxide					
Doxazosin		9–22	1–2			36,45
Guanethidine		2–8 days		0.008–0.01		36
Ketanserin		15	3–6	0.015–0.15		36
	Ketanserinol					
Alpha-Methyldopa		1–2	0.3–0.7	0.8–4.5	7.2–9.4	36
Minoxidil		2.8–4.2	2.8–3.6			36
Prazosin		2.5–2.9	0.6	0.001–0.075	>0.05	36,336
Reserpine (Rauwolfia)		1–2 weeks		0.0001–0.007		1778
Sodium Nitroprusside		0.1				28,339
	Cyanide			0.01–0.1		
	Thiocyanate			1–29	35–50	28,337

Table 2.36. *Antihypertensive drugs*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Benazepril				0.25		36
	Benazeprilat	3	8.7	0.30		
Captopril		1–2	0.7	0.05–0.5		338
Cilazapril		1–1.5	0.3–0.4			
	Cilazaprilat			0.005–0.01		36
Enalapril		1.3	1.7			
	Enalaprilat	35		0.02–0.08		36,339
Lisinopril		7–12	0.4–0.5	0.01		36,339
Perindopril		31	31	0.004		36,339
	Perindoprilat	29	9.3	0.005		
Quinapril		0.8		0.06–0.5		36
	Quinaprilat	1.9		0.2–1.8		
Ramipril		0.3–1	1.3			36
	Ramiprilat	1.1–4.5	6.14	0.002		

Table 2.37. *ACE inhibitors*

and pharmacokinetic studies of piracetam [1213,1214,2137] have been performed. The pharmacology of terazosin in association with methylclothiazide has been studied [1215]. The pharmacokinetics of terolidine was studied [2135]. Dal Bo et al. [1216] described an assay for vincamine in human plasma by HPLC.

Antianginal drugs

Several methods have been proposed for glyceryl trinitrate and metabolites [1217–1219]. Kinetic studies on isosorbide dinitrate and mononitrate were also performed [1220,1221].

Pharmacokinetic data of vasodilators and antianginal drugs are summarized in Table 2.38.

Diuretics

The analytical toxicology of these rather polar substances is difficult and requires special treatment, for example extractive alkylation, for their detection. Some are also abused and used in doping. General screening methods have been reviewed [1222–1230]. Clinical pharmacokinetic studies have been performed [1231].

Methods have been developed for the following substances: acetazolamide [1232], amiloride [866,1233,1234], bendrofluazide [1235], bumetanide including pharmacokinetics [1236,1237], canrenone [1238], chlorthalidone [1239], cicletanine [1240], clopamide [1241], cyclopenthiazide [1966], ethacrynic acid [1242], furosemide including pharmacokinetics [1234,1243–1245,1803], hydrochlorothiazide [1246,1247], indapamide [1248], spironolactone [1249,1250], tienilic acid [1251], triamterene [1252] and xipamide [1253,1254]. Pharmacokinetic data are summarized in Table 2.39.

Lipid regulating drugs

Rather old methods and pharmacokinetic studies are available for bezafibrate [1255], clofibrate [1256] and gemfibrozil [1257]. Pharmacokinetic data are summarized in Table 2.40.

Anticoagulants and antiplatelet drugs

A screening method using LC-MS for coumarin anticoagulants has been developed [1258]. One case of overdose has been reported with ticlopidine [1946]. Ethyl biscoumacetate can be assayed using LC-MS [1259]. Heparin kinetics and one case of overdose have been reported [1260,1261]. Monitoring of phenprocoumon by HPLC was described [1262]. Several methods for warfarin enantiomers have been studied [1263–1265]. Pharmacokinetic data are summarized in Table 2.41.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Buflomedil		1.5–4.3	1.3	0.2–20	30–275	339,1201,1995
Co-Dergocrin = dihydroergotoxine				0.0005–0.002		1203
Dihydralazine		2–4				1778
	Hydralazine	1–3.7	1–3.6	0.01–1.5		36,339
Dipyridamole		0.8–13	2	<1.4	4	36,337
Flunarizine		430	43	0.02–0.1		339
Hydralazine		1–3.7	1–3.6	0.01–1.5		36,339
Isoxsuprine		2–2.5		0.0005–0.02		36
Naftidrofuryl Oxalate		0.8–1.6	0.75–1	~0.1		36
Papaverine		1.5–2.2	0.2–1.5	0.2–0.6		36
Pentifylline						36,339
Pentoxifylline = Oxpentifylline		0.8–6	1.2–3.6	0.1		36,1212
	Hydroxyoxypentifylline			1.8		36,1212
Terolidine (withdrawn)		60	6.8	0.4–1.2	>0.6	36
Terazozine		11	0.8			339
Vincamine		2	0.6			339
ANTIANGINAL AGENTS						
Glyceryl Trinitrate		1–3 min	3.3	0.001–0.5		36
Isosorbide Mononitrate ISMN		3–7	0.7	0.1–1		36,338
Isosorbide Dinitrate ISDN		0.5–2	1.5–8.5	0.0008–0.2		36,339

Table 2.38. *Cerebral, coronary, peripheral vasodilators*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Acetazolamide		6–9	0.2	4–20	25	36,337
Amiloride		6–9	5.1	0.04		36
Bendrofluazide = Bendroflumethiazide		3–9	1.2–1.5	0.01–0.02		36
Bumetanide		1–1.5	0.1–0.5			36
Canrenone		10–20				1778
Chlorothiazide		15–27	0.3	0.4–200		36,75
Chlorthalidone		50–90	3–5	0.02–7.7		36,339
Clopamide		10	2.5	0.005		36
Ethacrynic Acid		0.5–1	0.1			36,339
Furosemide = Frusemide		0.7–1	0.1–0.27	0.2–0.3	>30	36,336
Hydrochlorothiazide		8–12	1–3	0.01–0.3		36,75
Hydroflumethiazide		12–27	6.4			36
Indapamide		10–22	0.85			36
Mefruside		3–16	4.4–7.4			36
Metolazone		4–20	1.6			339
Polythiazide		25	4	2–7		36,339
Potassium Canrenoate						1778
	Canrenone	10–20				1778
Spironolactone		0.1–1.3	14	0.05–0.2		36,339,1249
	Canrenone	10–20				1778
Triamterene		1.5–2.5	2.2–3.7	0.002		36
Xipamide		4.5–5.5	0.2–0.3	15–20		36

Table 2.39. *Diuretics*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Bezafibrate		0.9–4.8	0.3	3		36,339
Clofibrate		15–25	0.1–0.2	50–170		36,339
Gemfibrozil		1.3–2		16–23		36
Fenofibrate		22	0.9	5–15		339

Table 2.40. *Lipid regulating agents*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Acenocoumarol = Nicoumalone		8–10	0.2–0.3	0.03–0.1	0.1–0.15	36,45,337,339
Dicoumarol		7–70	0.15	8–30	>70	75,336,339
Heparin		0.3–2.5	0.04–0.07			36
Phenindione		5–6				36
Phenprocoumon		100–150	0.1	1–3	5	339
Ticlopidine		8–96		0.2–0.9		36,339
Warfarin		10–45	0.08–0.27	0.3–7	10	36,337

Table 2.41. *Anticoagulants and antiplatelet drugs*

GASTROINTESTINAL DRUGS

Antiulcer agents

Reviews of analytical methods for H_2-receptor antagonists [1266] and pharmacokinetics [1267] have recently been published. Analytical methods and pharmacokinetic data are available for cimetidine [1268], famotidine [1269], omeprazole [1270,2138], ranitidine [1271,1272], and roxatidine [1980,1981]. Pharmacokinetic drugs are summarized in Table 2.42.

Antiemetics, laxatives and other gastrointestinal drugs

Screening procedures for laxatives have been published [1273,1274]. Bisacodyl metabolites can be detected in urine [1275]. HPLC methods have been described for cisapride [1276], clebopride [1277], domperidone [1278], granisetron [1279,1280] and metoclopramide [1281–1283,2210]. The metabolic aspects of sennosides were discussed [1284]. Pharmacokinetic data are summarized in Table 2.43.

HORMONES, ANTIHORMONES AND ENDOCRINE DRUGS

Steroid hormones and antihormones

Recent reviews have been published on the screening of anabolic steroids used in doping [1285–1287]. Analytical methods have recently become available for danazol [1288], diethylstilbestrol [1289], various estrogens after pre-column derivatization [1290], furazabol [1291], nortestosterone [1292], stanazolol [1293], testosterone [1294], trenbolone [1295,1296], tamoxifen [1297,1298] and toremifene [1298], zeranol [1299] and propylthiouracil [1300]. Other hormones, such as oxytocin [1301] and growth hormone [1302], can be monitored by RIA. Pharmacokinetic data are summarized in Table 2.44.

Corticosteroids

Screening methods and pharmacokinetic studies for several corticosteroids have been published [1303–1305]. The plasma determination of beclomethasone [1306], budesonide [1307], cortisone [1308], dexamethasone [1309], flumethasone [1310], prednisone and prednisolone [1311] as well as triamcinolone [1312] has been described. Pharmacokinetic data are summarized in Table 2.45.

Hypoglycemic agents

A review of several sulfonylurea drug assays [1313] and the pharmacokinetics and pharmacodynamics of oral hypoglycemic agents [1314] were published.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Cimetidine		1–4	0.8–1.4	0.5–1	>1.25	36,75,337
Famotidine		2.2–3	1.3			339,1778
Nizatidine		1.3–4	1.2	0.07–0.7		339
Ranitidine		2–3	1–2	0.15–0.25		336,339
Roxatidine		4–6				339,1778

***Table 2.42**. Antihistamines H_2*

Compounds Parent drug	Main metabolites (h)	Elimination half-time (l/kg)	V_D	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Cisapride		7–10	1.9–2.4	0.05–0.1		36,339
Diphenoxylate		1.9–3.1	3.8–5.4	0.01		36,75,339
	Diphenoxylic Acid DPA	3.4–5.4				36
	Hydroxydiphenoxylic Acid HDPA					36
Domperidone		7–8	5.7	0.015–0.02		36,338
	Hydroxydomperidone					36
Dronabinol = Tetrahydrocannabinol		14–38	4–14	0.001–0.02		75,339,801
Granisetron		2.6–6.8	3.3	0.02–0.03		36
Loperamide		10–12		0.002–0.003		36,339
	N-Desalkylloperamide					36
Metoclopramide		2.6–5.4	2.2–3.4	0.04–0.1	0.1–0.2	36,337
Omeprazole		0.5–1.5	0.3–0.4			36

***Table 2.43**. Antiemetics, laxatives and other gastrointestinal agents*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Danazol		2.6–29		0.1–0.15		36,339
Diethylstilbestrol = Stilbestrol			5			36
Growth Hormone = Somatropine		0.2–0.5				36
Medroxyprogesterone MPA		30	0.3–0.6	0.001–0.09		36,339
Oxytocin		2–10 min	0.3	30–150 ng/l		36
Propylthiouracil		1–3	0.4	4–5		36,339
Tamoxifen		7 days		0.3		36

Table 2.44. *Hormones and antihormones*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Beclomethasone		15				339
Betamethasone		5.6	1.4			36,339
Budesonide		2.7	4.4			36,339
Cortisone		1–1.5	0.3			36
	Hydrocortisone	1–2	0.4–0.7	end.0.1–0.25		36
Dexamethasone		2.5–4	0.6–0.8	0.1–0.17		36,339
Hydrocortisone		1–2	0.4–0.7	end. 0.1–0.25		36
Methylprednisolone		2.5	0.8			339
Prednisolone		2.2	0.6			339
Prednisone		3.6	0.9–1.0			339
Triamcinolone		1.5–5	0.9–1.8	0.003–0.004		36

Table 2.45. *Corticosteroids*

Analytical methods were proposed for glibenclamide or glyburide [1315,1316], gliclazide [1317], glipizide [1318], tolbutamide with its metabolite carboxytolbutamide [1319], glimepiride [2164], and zopolrestat [2165]. Insulin has been used for suicide and homicide [1320]. Pharmacokinetic data are summarized in Table 2.46.

CHEMOTHERAPEUTIC DRUGS

Many of the chemotherapeutic drugs are not frequently encountered in acute poisonings, but are frequently quantified in therapeutic drug monitoring.

Antimicrobials

HPLC methods for antibiotics have been reviewed [1321]. Other general procedures for the screening of antibiotics or families of antibiotics have been published, such as procedures for antibiotics in animal feed [1322] and amphoteric β-lactam antibiotics [1323], LC-MS methods for anthracycline antibiotics [1324], and penicillins and cephems [1325]. Clinical pharmacokinetic studies on various groups of antibiotics were published [1326–1329]. Pharmacokinetic properties are summarized in Table 2.47.

Analytical methods are available for the following substances: adriamycin [1330], amoxacillin [1331], amphotericin B [1332], aspoxicillin [1333], cefepime [1334], ceftazidime [1335], cephalosporin SCE-2787 [1336], cephapirin [1337], chloramphenicol [1338,1339], ciprofloxazine [1802], dapsone [1340], doxycycline [1341], furazolidone [1342], gentamicin [1343,1344], isepamicin [1345], isoniazid [1346,1347], minocycline [1348], neomycin B [1349], ofloxacin [1350, 2154], oxytetracycline [1351], penicillin G [1352], penems SCH 29482 and FCE 22101 [1353], plicamycin [1354], rapamycin [1355,1356], rifapentine [1357], rufloxacin [1358,1359], spectinomycin [1360], spiramycin [1361], sulfamethazine [1362–1364], teicoplanin [1365], tiamulin [1366], ticarcillin [1367], tobramycin [1344], vancomycin [1368,1369], and the new fluoroquinolone derivative DV-7751a [2155].

Antifungal drugs

Analytical and pharmacokinetic studies of fluconazole were performed [1370–1372]. Köppel et al. [1373] developed a TDM method for flucytosine. A HPLC method for itraconazole [1374], pharmacokinetic studies of ketonazole [1375], terbimafine [2139,2140], and an analytical method for the antifilarial drug UMF-058 [1376] are available. Pharmacokinetic studies on omoconazole and sertaconazole were performed [2150]. Pharmacokinetic data are summarized in Table 2.48.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Buformine		1.8–7.2	1.5–3.1	0.2–0.6	3.2	75,339
Chlorpropamide		25–60	0.1–0.3	70–250	200–700	36,75
	2-Hydroxychlorpropamide					
Glibenclamide		1.5–10	0.1–0.2	0.03–0.05		36
Glibornuride		8.2	0.15–0.37	2		36,339
Gliclazide		6–14	0.35	1.5–3.9	35	36,1994
Glipizide		2–4	0.14	0.02–0.7		36
Gliquidone		16	0.14–0.17	0.5–0.7		36
Glymidine		2–10		40–150		36
Insulin		4–9 min	0.08–0.6	4–80 mU		36,339
Metformin		1.5–4.5	0.9–3.9	0.1–2.3	>80	36,75
Tolazamide		7				339
Tolbutamide		4–12	0.1–0.2	60–100	500	36,337
	Carboxytolbutamide					

Table 2.46. *Antidiabetic drugs–hypoglycemic agents*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Amikacin		2–3	0.2–0.25	3–6		36
Aminosalicylates		0.8–1	0.2	0.6–4		34
Amoxycillin		1	0.3	1.0–1.5		36,336
Ampicillin		1–2	0.4	1–15	10–35	36,336
Ansamycin				0.005–0.15		336
Azlocillin		1	0.2	500		36
Aztreonam		1.7	0.2	1–250		36,337
Bacitracin*		1.5				34
Benzylpenicillin		0.5–1	0.2–0.7			36
Cefaclor		0.5–1	0.4	13–900		36,337
Cefotaxime		1	0.4	1.7–25		34,45,336
	Desacetylcefotaxime	1.5		0.1–3		36
Cefsulodin		1.5	0.26	20–100		36,337
Ceftazidime		1.8–2.2	0.22	20–200		36,337
Ceftriaxone		8	0.15	15–75		337,339
Cefuroxime		1.4	0.28	0.5–180		337,339
Cephaloridine		1.4	0.22	0.5–50		36,337
Cephamandole		0.5–1.5	0.25	12–140		36
Cephradine				0.5–50		337
Chloramphenicol		1.7–12	0.6–5.1	5–20	>20	75,337
Chlortetracycline		5–6	2	4–12		36
Ciprofloxacin		5	2.1	0.4–5		336,339
Clindamycin		1.5–3.5	1.1	0.002–0.8		36,339
Cloxacillin		0.5–1	0.14	5–85		36,336
Dapsone		12–48	1.9	0.5–5	15–20	36,336,339
	Monoacetydapsone MADDS					36
Doxycycline		18–22	0.9–1.8	5–10	30	36,336
Erythromycine		1–1.5	0.75	0.5–12	12–15	36,336
Ethambutol		10–15	3.9	0.5–8		36

Flucoxacillin		0.4–1.5	8–21	0.05–500		36
Gentamicin		1–4	0.2	0.5–10	2–12	36,336
Imipenem		1	11–12	0.01–250		36
Isoniazid		0.5–2	0.6–0.8	0.2–10	20	36,336
Kanamycin		2.2–2.5	~0.3	~4	30–35	36,75
Lincomycin		4.4	0.4	2.5–5		36
Minocycline		12–16	0.96–1.27	4–12		36
Nalidixic Acid		1.5	0.4	20–50		36
Neomycin		2	0.25	5–10		36
Netilmicin		2.5	0.3	2–8	>12	34,36,337,339
Nitrofurantoin		0.3–1	0.6	0.5–2	3–4	36,337
Ofloxacin		4.9–6.9	1–2.5	0.05–7		36,337
Pefloxacin		5–10	1	0.1–10	25	337,339
Penicillin G (benzyl)		0.5–1	0.2–0.7	1–10		36
Polymyxin B		4.4		0.5–4		339
Prothionamide		1.5–2.1		0.5–8		36,337
Pyrazinamide		10–24		30–75		36,337
Rifampicin		1–6	1	0.5–10		36,339
	Desacetylrifampicin			tot 0.1–10	tot 2–12	337
Silver Sulphadiazine		10–12	0.36	10–150		36
	Silver (Ag)			0.2–0.3		36
Streptomycin		2.4–9	0.26–1.4	0.4–4		36,339
Sulphamethoxazole		6–20	0.2	40–200	>200	36,337
	N–Acetylsulfamethoxazole					36
Teicoplanin		32–176	0.9	25–40		36
Tetracycline		6.8–8.5	1.3	5–10	0.5–30	36,339
Ticarcillin		1–1.2	0.2	25–250		36
Tobramycin		2–3	0.3	0.5–12		36,336
Trimethoprim		9–17	1–1.42	1.5–10	15–20	36,337
Vancomycin		5–11	0.6	10–35	40	36,337

*Not absorbed (topical).

Table 2.47. *Antimicrobials*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Amphothericin B		24–48	4	0.025–3.5	5–10	36,337
Clotrimazole			1			36
Fluconazole		30	0.55–0.65	6–20		36
Flucytosine		2.5–6	0.7–1	25–100	>100	36,336
Griseofulvin		9.5–21	1.2–1.4	0.5–2		36
Itraconazole		20	10.7	0.1–100		36
Ketoconazole		6–10	0.4	1–10		34,36
Miconazole		24.1	20	0.4–32		36
Nystatin				3–6		36

***Table 2.48**. Antifungal drugs*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Acyclovir		3–4	0.7	0.5–2		36,337,339
Amantadine		12–40	4.4–10.4	0.4–0.9	20–30	36,75
Ganciclovir		2–5	0.5–1.7	0.2–12.5	3–20	36,337
Idoxuridine (IDU)		0.5		<40		36
Interferon Alpha		3–4	0.4			36,339
Rimantadine		29	25			339
Vidarabine		1–4.5	0.7	3–10		36,339
Zidovudine = AZT		0.3–1.5	1.1–1.6	0.1–1.5	2–3	36,336,339

***Table 2.49**. Antiviral drugs*

Antiviral drugs

A review of analytical methods for antiviral drugs in biological specimens was published in 1990 [1377]. The chromatographic analysis of methylmercaptopurine riboside was studied in human plasma and urine [1380]. Pharmacokinetic studies of nucleoside analogues [1378], the interferons [1379] and zidovudine (AZT) [1381] were reviewed. Pharmacokinetic date are summarized in Table 2.49.

Antimalarial drugs

In contrast to other chemotherapeutic agents, these drugs are quite frequently observed in acute poisonings. Analytical methods and reports of acute poisoning have been published for amodiaquine [1382], chloroquine and desethyl metabolite [1383–1385], halofantrine and metabolites [1386–1388], hydroxychloroquine [1389,1390], mefloquine and metabolites [1391,1392,1740], pamaquine [1393], primaquine [1393,1394], proguanil [1395,1965] and quinine [1396,1397]. Pharmacokinetic properties are summarized in Table 2.50.

Antiparasitic, antiprotozoal and antiamebiasis drugs

Only a few methods for the determination of small amounts in biological material will be cited, such as ipronidazole, ronidazole and dimetridazole with metabolites [1398], carbadox [1399], ivermectin [1400,1401], metronidazole [1402], nicarbazin [1403] and nitrofurazone [1404]. Pharmacokinetic data are summarized in Table 2.50.

Anthelmintics

Many methods are available. As these substances do not belong to a single chemical family, no general screening method is available. For benzimidazoles, a multiresidue method by HPLC and GC-MS is available [1405]. Methods as well as pharmacokinetic data were published for albendazole [1406,1407], diethylcarbamazine [1408,1409], emetine [1410], levamisole [1411,1412], mebendazole [1413–1415], piperazine [1416], praziquantel [1417,1418] and suramine [1419]. Pharmacokinetic data are summarized in Table 2.50.

Anticancer drugs and immunosuppressants

A review on the chromatographic analysis of anticancer drugs was recently published [1420]. Analytical methods or pharmacokinetic studies on the following substances are also available: aminogluthemide [1421], azathioprine [1422], chloracetaldehyde as metabolite of oxazophosphorine [1423], carboplatin = CBDCA and cisplatin = cis DBP [1424–1426,1818,2157], cyclosporine [1427], 5-fluorouracil [1428], indoloquinone EO9 [1429], melphalan [1430],

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
ANTIMALARIAL DRUGS						
Amodiaquine		3.5–50	36	0.015–0.04		34,36,339
Chloroquine		30–60 days	100–200	0.02–0.5	>1	36,337,339
	Desethylchloroquine					75
Halofantrine		1–4 days		0.002–0.035		36
Hydroxychloroquine		3–18 days	50	0.01–0.4	>60	36,75,339
	Desethylchloroquine					75
Mefloquine		15–33 days	16–25	0.6–2.6		36
Primaquine		4–10	3–4	0.15		36
	Carboxyprimaquine	16	3.6	1.4		36,75
Proguanil		11.8–23.4		0.17–0.37		36
	Cycloguanil	1.3–3.3		0.015–0.06		36
Pyrimethamine		35–175	2.2–3.4	0.07–0.25	>6	36,112,339
Quinine		7–12	1.2–3	2.5–4	>10	36,337,339
ANTIPARASITIC, ANTIPROTOZOAL AND ANTIAMEBIASIS DRUGS						
Emetine				0.005–0.07		75
Metronidazole		7.9–9.8	0.8–1	10–30	200	36,337
Nitrofurantoine		0.3	0.8	1.8		339
Suramin		36–60 days	20–80	20–150		36
Tinidazol		12–14	0.64	0.5–58		36
ANTHELMINTICS						
Albendazole		8.5				36
	Albendazole Sulphoxide			0.22–5		36
Diethylcarbamazine		5–13	1.5–5.3	0.1–0.2		36,45
Ivermectin		12		0.02–0.06		36

Levamisole		4–6	1.4–1.7	0.7–1.4		36,45
	p-Hydroxylevamisole					36
Mebendazole		1.4–5.5	1–1.2	0.05–0.1		36
Metriphonate = Trichlorfon = Dipterex		1.2			0.2–310	36,1570
	Dichlorvos = DDVP					
Oxamniquine		1–2.5		0.3–2.2		45
Praziquantel		1–8				36,45
Thiabendazole		1.2	2.8	2–6		36,45
	5-Hydroxythiabendazole					

Table 2.50. *Other chemotherapeutic agents, antimalarial drugs*

methotrexate [1431], mitomycin analogue KW 2149 [1432], substance S9788 [1433], tacrolimus or FK 506 [1903], and taxotere [1434]. One case of suspected cis-platin overdose has been described [1818]. Pharmacokinetic data are summarized in Table 2.51.

ENVIRONMENTAL CHEMICALS

There are so many potentially toxic environmental chemicals, that it is impossible to provide an extensive survey of the literature. Therefore, only the most important chemicals have been selected.

Inorganic chemicals

Several handbooks on the toxicity and analytical toxicology of inorganic compounds (essentially metals) are recommended [1435–1437]. A good summary of the trace element reference values in human tissues was published by the European Community [1438]. General (screening) methods for the simultaneous determination of several elements have been published [1439–1448, 1904], with reference to acute poisonings [1446] and dietary intake [1449,1450] as well as rare earth elements like dysprosium, europium, ytterbium and yttrium [1451].

Methods can be proposed for the following substances: aluminium [1452–1456] with particular sampling precautions [1453], arsenic [1457,1810] including speciation by ion chromatography [1458] and dietary intake [1459], beryllium [1444,1460,1956], bismuth [1461,1462], boron [1463,1940], cadmium [1464,1465], chromium [1466], copper [1467], mercury and organomercurials [1468–1472] including release from dental material [1473–1476], iron [1477], nickel [1478–1480], lead [1481–1485] and lead tetraethyl [1848], platinum [1486], ruthenium [1487], selenium [1488,1489], tin and organotins [1490], thallium [1491], uranium [1492] and vanadium [1493–1496]. Analytical methods for silicium derivatives, such as silicone defoamer [1497] and asbestos [1498,1499,2216,2217] have also been investigated.

Anions

The analytical toxicology of anions is difficult, but it has improved with the introduction of ion-chromatography [139,178], capillary electrophoresis [1793, 1794,1906,2160] and TLC [2159]. Reports of overdose were published and new methods discussed for azide [1500], borate [1940], bromate [1501], cyanide [1502–1505,2161], fluoride [1506,1507,1942] nitrates and nitrites [1508,1509] with special care for the determination of methemoglobinemia [1508], oxalates [1510], sulfides [1511,1512] and thiocyanates [1513–1515,2162]. Pharmacokinetic data on inorganic compounds have been summarized in Table 2.52.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Therap. range	 Toxic range	Ref.
Aminoglutethimide		10.3–13.3	1.3	0.05–27.8		36,45
Amsacrine		3.3–6.3		0.1–5.5		36,337
Azathioprine		3–5		0.05–0.3		36
	6-Mercaptopurine	0.9–1.5	0.1–1.7	0.03–0.08	1–2	337
Bleomycin		4	0.28	55–130 units/l		36
Busulphan		2–3	1			36
Carboplatin (CBDCA)		1.5		10–25		36,336
	as Pt (Metabolite)	6–24		0.5–5	>30	336
Carmustine (BCNU)		0.3–0.4	3.3–5.1	0.5–1		36
Chlorambucil		1–2	0.9			36
Cisplatin (cis DDP)		0.3–0.5	0.5	1–5		36,336,339
	as Pt (Metabolite)	44–190		0.5–5	>30	36,336
Cyclophosphamide		4–10	0.6–1			36
Cyclosporin A		27	1.5–7	0.05–0.4	0.45	36,337
Cytarabine		1–3	2.2	0.05–0.5		36,336,339
Daunorubicin		18–27	23			339
	Daunorubicinol	26				36
Doxorubicin = Adriamycin		24–48	25	0.006–0.02		36,337
Epirubicin		39	50	0.01–0.05		336,339
Etoposide		4–8	0.35	2–6		36,337,339
Fluorouracil		0.1	0.1–0.4	0.05–0.3	0.4–0.6	36,337
Melphalan		1–1.5	0.4–0.8			36
6–Mercaptopurine		0.9–1.5	0.1–1.7	0.03–0.08	1–2	36,337
Methotrexate (MTX)		8–10	1–3	0.04–0.4	>0.4	36,75,336
	7-Hydroxymethotrexate					36
Mitozantrone		4–215				36
Vinblastine		20	8–27	0.25–0.4		36,337
Vincristine		85	8.4	0.3–0.4		36,337

Table 2.51. *Anticancer and immunosuppressant drugs*

Compounds Parent drug		Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) normal range	 Toxic range	Ref.
Aluminium	Al				0.0003–0.0075 dial. 0.03–0.3*	0.1–0.6	75,337,1438
Antimony	Sb		38 days		0.00001–0.0017	4–5	75,1438
Arsenic	As		7 days	0.2	0.0004–0.0012	0.1–10	75,337,1438
Barium	Ba		3.6 days		0.00047–0.0024**	1–8	75,1438
Beryllium	Be				0.00003–0.00027		1438
Bismuth	Bi		5 days		0.00012–0.0008**	>0.1	75,337,1438
Borate	BO_3^{3-}		12–27	0.17–0.5	0.2–2	381–7900	75,1940
Boron	B				0.0002		1996
Bromide	Br^-				0–30	500–1000	337
Cadmium	Cd		16 years		0.00004–0.00036	0.015–0.05	337,1438
Chromium	Cr				0.00004–0.00041		1438
Cobalt	Co				0.00008–0.0004	0.8	75,1438
Copper	Cu				0.6–1.37	2.5–25	75,1438,1467,2010
Cyanide	CN^-		44–66		NS 0.004** S 0.006**	0.5–50**	28,75,337
		Thiocyanate SCN^-			NS 1–4** S 3–12**	35–53**	28,337
Fluoride	F^-		2–9	0.5–0.7	0.08–0.15	0.5–1770	75,337,2008
Gold	Au		5–16 days	0.1	0.002–0.08 µg/l 3–8 *	10–15	75,337,1438
Iridium	Id				0.0002–0.018 µg/l		1438
Iron	Fe				14–35 µmol/l (0.79–1.96)	2.7–25.5	75,1996
Lead	Pb		0.4–3.6 years		0.0001–0.0005	>0.4	337,1438,1996
Lithium	Li		7–20		0.5–1.5 mmol/l*	>2 mmol/l	337,1996
Magnesium	Mg				0.7–1 mmol/l		1996
Manganese	Mn				0.0003–0.0009	0.02–0.075	75,1438

Mercury	Hg		24days 52 days (MeHg)	0.001–0.010**	0.4–2.1 0.6–6(MeHg)	75,1438
Molybdenum	Mo			0.002–0.005		1437
Nickel	Ni			0.0002–0.003	3	1438,1996
Nitrate	NO_3^-			<50 µmol/l	15–58	75,1996,2011
		Methemoglobinaemia		0.01–0.5% **	50–80%**	75,1996
Nitrite	NO_2^-			<50 µmol/l	0.5	75
		Methemoglobinaemia		0.01–0.5%**	50–80%**	75,1996
Oxalate	$C_2O_4^{2-}$			1.4–2.4	18–110	75
Platinum	Pt		59–73	0.0001–0.003 0.5–5*	tox. >30	36,336,1486
Potassium	K			3.4–4.5 mmol/l		1996
Selenium	Se		69–77 days	0.05–0.1	>3	1437,1438
Silicon	Si			2–290		31
Silver	Ag			0.06–0.3 µg/l		1438
Sodium	Na			135–143 mmol/l		1996
Sulfide	S^{2-}			<0.05	0.9–3.8	1997
Thallium	Tl		2 days	0.00002–0.00034	0.1–0.9	75,339,1438
Thiocyanate	SCN^-			NS 1–4** S 3–12**	35–53 **	28.337
Tin	Sn			0.005	0.1–1.6 (U)[a]	1436,2021,2023
Tungsten	W			0.000004–0.00035		1438
Vanadium	V			0.00007–0.05		1437,1438
Zinc	Zn		0.5–1.5 years	0.58–1.5	1.5–42	75,339,1438

* Therapeutic range; **whole blood; NS = non smokers; S = Smokers; (U) = Urine.
[a]From organotin compounds.

***Table 2.52**. Inorganic compounds*

Pesticides

Many acute poisonings occur from pesticides, especially in developing countries. Some pesticides circulate at rather low concentrations in blood, and can be easily missed, although clinical symptoms are very characteristic. Biological parameters, like cholinesterases in carbamate and organophosphate poisonings may be very helpful [1539,1540]. A general introduction to the analytical toxicology of pesticides [1516] and a paper on the unjustified fear of pesticides, if applied correctly [1517] have been published. Data on daily intakes in the US are available [1518–1520]. Concern was recently raised in the UK regarding the health effects due to organophosphate sheep dipping [1953,1954]. General screening methods for different groups of pesticides have been developed [1521,1523–1526]. Immunoassays are also available [1522].

Methods have been proposed for carbamates [1527,1528], chlorinated pesticides or organochlorines [1529–1533], organophosphates [1534–1538,1807] including military nerve gases [1538] and other chemical warfare agents like tear gases [1835] and QNB [1872]. A HPLC assay for one of the antidotes (oximes) or mixtures of oximes and atropine was also published [1541,1987] as well as for pyrethroids [1542,1814].

Analytical methods have recently become available for the following pesticides: aldicarb [1543,1544], amitraz [1545], azinphos-ethyl [1546], benalaxyl [1547], benomyl [1548] and its degradation product methyl-2-benzimidazole carbamate [1549], bupirimate [1550], captan [1551], captafol and folpet [1552], carbofuran [1553], chlorothanil [1554], chlorpyrifos [1555], demeton-S-methyl [1556], endrin [1557,1558], fenitrothion [1559,1560,1773], formothion (as dimethoate) [1561], isobenzan [1562], isopropylmethylphos [1563], lindane [1564], malathion [1565], methidathion [1566], methomyl [1567], methylparathion [1928], mirex [1568], propoxur [1569], trichlorphon [1570], α and β-hexachlorocyclohexanes [1571], α-cypermethrin [1572], tetrametrin [1573], N,N′-diethyl-m-toluamide (m-DEET) which is an insect repellent [1574,2163] and RH-5992, an ecdysone agonist [1575].

Rodenticides

A general method for eight anticoagulants used as rodenticides has been investigated [1576]. Case reports have been published with brodifacoum [1577, 1578], d-CON rat poison [1579] and tetramethylene disulfotetramine [1815].

Herbicides and plant growth regulators

Many herbicide poisonings occur (mostly suicide attempts) especially in Japan with paraquat [1842]. Methods have been developed for atrazine [252], chlormequat [1580], dinitroanaline derivatives [2166], diquat [1581], diuron [1582], glyphosate [1583,1584], glufosinate [1584] and bialaphos [1584], MCPP [1585], monochloroacetate [1586,1945], paraquat [1587–1591,1925] and

propachlor [1592]. Pharmacokinetic data on pesticides have been summarized in Table 2.53.

Solvents

As most solvents are volatile, they can normally be analyzed in one run in a general screening by head-space techniques using GC or better GC-MS [1593–1597,2167,2168]. NMR spectroscopy can also be used [1921]. The clinical toxicology of these substances has been reviewed [1598]. The combination of alcohol and driving is a critical problem [1599] and congeners can be used to identify the beverages drunk [1600]. Methanol poisoning is not uncommon and analytical methods have been developed [1601–1606]. In acute poisonings, potassium is a useful parameter to monitor [1608]. Acetone and other ketones, like methyl-ethylketone and cyclohexanone, have been monitored in acute poisonings [1609,1610]. Acetonitrile poisoning is not rare [1611,1612]. A method for the determination of dimethylsulphide in biological specimens has been developed [1613]. Several papers dealt with poisonings due to chlorofluorohydrocarbons (CFCs) [1614–1617] and polychlorotrifluoroethylene [1873]. Chloroform can be monitored by head-space GC [1618], and halogenated hydrocarbon mixtures by purge and trap capillary GC [1619]. Several other halogenated solvent poisonings were studied, including dichloromethane [1620], 1,1,1 trichloroethane [1621], 1,3 dichloropropane and 1,2 dichloropropene [1622], chlorobenzenes [1623] and vinylidene chloride [1624].

Volatile hydrocarbons such as the following are frequently seen in toxicology departments: benzene [1625,1626], petroleum fuel [1627], kerosene [1628], liquid petroleum gas [1629], thinner components [1630], gazoline [2219], light petroleum ingested by "fire eaters" [1631,1632], hexane and metabolite 2,5-hexanedione [1633], pseudocumene [1634,1696] and toluene [1635,1636]. Car fuel additives like tetraethyl lead may also be the cause of acute poisonings, as in Poland [1848]. Nitropropane is another substance of toxicological concern [1637]. Nitroethane from artificial fingernail remover can lead to poisoning [1939].

Glycols, other polyalcohols and ethers

Various analytical methods applicable to biological specimens have been developed for ethylene glycol and diethylene glycol [1686,1689,1784,1961, 2169,2170] and also glycolic acid [1841], 1,3-butylene glycol [1690], propylene glycol [1691], butylglycol [1692], ethylene glycol monobutyl ether [1693], thiodiglycol [1694] and glycerol [1695]. 2-butoxyethanol and butoxyacetic acid were studied by GC-MS [2171]. Methyl tert butyl ether (MTBE) was measured in blood [2172].

Fluosol, a fluorinated compound, sometimes used as a blood substitute, can give rise to false positive tests for ethylene glycol [1944]. Pharmacokinetic data on solvents have been summarized in Table 2.54.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Normal or asymptomatic range	 Toxic range	Ref.
Aldicarb					11	2005
Aldrin		50–167 days		0.0007–0.002	0.1–0.3	75
	Dieldrin	2–12 months	13–69	0.001–0.02		75
Azinphos-Ethyl					n.d.–370	1546
Brodifacoum					0.09–0.16	1576,1577
Bromindione						
Bromodiolone					0.05–0.25	1576
Bromoxynil					350	2017
Carbaryl					14	75
	1-Naphthol					
Carbofuran					17	2006
Chlorates					0.17	2022
	Methemoglobinaemia			0.01–0.5% **	50–80%**	75,1996
Chlordane		88 days		0.01–0.2	1–5	75
Chlordecone (Kepone)				0.005–0.03	0.6–32	75
Chlorophacinone					0.1–14	1576,2020
Chlorophenoxyacetic Acid					200	337
Chlorpyriphos					0.2	1516
Coumafuryl					0.05–0.25	1576
Coumatetralyl					0.025–0.125	1576
Cyfluthrin					10	2003
DDT				0.005–0.04 0.57–2.9 (W)		75
	DDE			0.09–0.2		2018
DEET (Diethyltoluamide)					240	20
Demeton-S-Methylsulfoxide = Metasystox R = DSMSO					0.5–50	2019
Diazinon					0.7–227	75,2016
2,4-Dichlorophenoxyacetic Acid = 2,4 D				0.2–35	58–820	75,337,1997

Dieldrin		2–12 months	13–69	0.001–0.02	0.01–0.05	28,75,2018
Difenacoum					0.025–0.125	1576
Dinitro-o-cresol=DNOC		5–6 days		1.4–4.3	20–80	75,337
Diphacinone					0.1–2	1576
Diquat					0.06	75
Endosulfan					0.6–2.8	2001
Endrin				<0.003	0.01–544	28,1558
Fenitrothion					1–1.1	1516
	p-Nitro-m-cresol				0.5–0.9 (U)	1516
Fluoroacetic Acid					10	75
Lindane (HCH)		21		0.001–0.07	0.2–0.8	28,75,2018
Malathion		2.9		0–3.5	100–1880	75
	Malathion Mono-carboxylic Acid				223 (U)	1516
Methamidophos					130	2012
Methomyl					0.5–35	1567,2009
Methylchlorophenoxyacetic Acid = MCPA					505	2017
Mevinphos					340	1516
Paraquat		12–120			0.05–60	75,337
Parathion				0.004–0.2	0.5–34	75
	Paraoxon				6	1516
	p-Nitrophenol				3–8 (U)	1516
Phosphamidon					40	2013
Propoxur					48	LNS
Protampephos					0.6	2004
Trichlorfon = Metriphonate = Dipterex		1.2			0.2–310	1570
	Dichlorvos = DDVP					
2,4,5-Trichlorophenoxyacetic Acid = 2,4,5 T		11–23	6.1	40–88	182 (+ 2,4-D)	75

*Due to rapid metabolism, many o-phosphate pesticides are extremely difficult to detect in blood. Therefore cholinesterase activity determination either in plasma or erythrocytes (RBC–AChE) or both in living patients is essential. **Asymptomatic workers.
(U) = Urine; (W) = workers.

Table 2.53. *Pesticides**

Compounds Parent drug	Main metabolites	Elim. half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Normal or asymptomatic range	 Toxic range	Ref.
Acetone		3–5	0.8	>10 fasting/diabetes 100–700	2500	75
Acetonitrile						
	Cyanide	44–66		NS 0.004** S 0.006**	0.5–50**	28,75,337
	Thiocyanate			NS 1–4** S 3–12**	35–53**	28,337
Benzene		1–3		0.008–0.2	0.9–38	75
Benzyl Alcohol					66–148	75
	Benzoic Acid					
Carbon Disulphide		<1		0.1–0.7		75
Carbon Tetrachloride = Tetrachloromethane				0.07	20–260	75,1998
Chlorobenzene					11.3	LNS
Chloroform		1.5	2.6	0.004–0.35 anaesth. 60–182	10–48	75
Cyclohexane				0.03–0.30		75
	Cyclohexanol					
Dichloromethane		0.6		1–12	200–510	75
	COHb			5%		1998
		11–14		504–560		75
Dioxane		1		12		75
	HEAA	3		10		75
Ethanol		2–14	0.5–0.6	0–25	1000–2000	75,337
	Acetaldehyde			>0.2	acute:0.9–1.3 chron.:1.7–2.5	75
Ether				anaesth. 500–1500	600–3750	75
	Ethanol	2–14	0.5–0.6	0–25	1000–2000	75,337
	Acetaldehyde			>0.2	acute:0.9–1.3 chron.:1.7–2.5	75

2-Ethoxyethanol						1998
	Ethoxyacetic Acid			50 (W) (U)		1998
	Ethylene Glycol	3–60	0.5–0.8		300–4300	75
Ethyl Acetate						
	Ethanol	2–14	0.5–0.6	0–25	1000–2000	75,337
Ethylene Glycol		3–60	0.5–0.8		300–4300	75
	Oxalate			1–2.4	>20	28
Hexane				0.2–0.4		75
	2-Hexanol					
	2,5-Hexanedione			0.9		75
Isopropanol		2.5–3	0.6	>10 (W)	3300	75
	Acetone	3–5	0.8	40–160	1200	75
Methanol		2–24	0.6	<1.5	0–4000	75
	Formic Acid			5	8–134	75
Methyl Ethyl Ketone= 2-Butanone = MEK				0.5–9.6 (W)		75
Methyl Isobutyl Ketone = 4-Methyl-pentane-2-one				3.5 (W)		1998
Methyl n-Butyl Ketone = 2-Hexanone				1.2		75
	2,5-Hexanedione			0.9		75
2-Methylpentane = Gasolin					52	75
Nitrobenzene						
	Methemoglobinaemia			0.01–0.5% **	50–80 %**	75,1996
	Aniline					
	p-Nitrophenol					
Propylene Glycol		2–5	0.55	6–711 (ther.)		75
Tetrachloroethylene		33–72	8.2	0,4–3.1 (W)	4–115	75,2015
	Trichloroethanol			5 (W)	40–70	337,1998
Toluene		72		0.4–1.2 (W)	10–20	75
	Benzoic Acid					
1,1,1-Trichloroethane		53		1.4–6.5 (W)	1.5–720	75
	Trichloroethanol			5 (W)	40–70	337,1998
Trichloroethylene		30–38		1–7 (W)	3–110	75
				33–90 anaesth.		
	Trichloroethanol			5 (W)	40–70	337,1998
Xylene		20–30		1–2.1 (W)	3–110	75

(W) = Workers; (U) = urine; NS = non smokers; S = smokers. **Whole blood.

Table 2.54. *Solvents*

Other environmental chemicals

Many other environmental chemicals are of concern in the analytical toxicology laboratory. Some general screening methods for organic pollutants have been described [1658,1659].

Aldehydes. There are many aldehydes for which analytical methods have been developed. They include for example, acetaldehyde [1660,1661], acrolein [1662], formaldehyde including the metabolite formate [1663–1666], and malonaldehyde [1667].

Amines. Several methods for the detection of volatile and non volatile amines [1668] have been proposed, such as dimethylamine and trimethylamine and the oxide [1669], 4,4-methylenedianiline [1670], paraphenylene diamine [1671], chloronitro-aniline and 2,4 dinitroaniline [1672], various anilines [1673] and dibutylamine [1674]. 4,4-methylene diphenyldianiline was determined in workers exposed to diphenyldiisocyanate [2142].

Carcinogens. Methods have been developed to detect polyaromatic hydrocarbons in biological materials, for instance diesel exhaust [1697] and other polyaromatics [1698,1699,2173,2174]. Nitroso-compounds are difficult to analyze [1700–1702].

Disinfectants and other common chemicals. Methods for the detection of phenol [1703], bromhexine [1704], chlorhexidine [1705], denatonium benzoate (Bitrex®), a very bitter substance in OTC drugs [1706], phthalates [1707, 1708], initiators and stimulators of polymerization processes, as in dental methyl methacrylate [1780], were proposed.

Persistent organochlorine compounds. A review on persistent chlorinated hydrocarbons in human tissues has been published [1638]. Pentachlorophenol and impurities have been investigated [123,1639–1641]. Polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) are another topic of "emotional chemicals" with difficult analytical toxicology [123,1642–1652,1989,2175]. Analytical problems associated with polychlorinated biphenyls and terphenyls are not easy [1653–1657,1959,2176–2178]. Pharmacokinetic data on environmental or common chemicals and natural toxicants are summarized in Table 2.55.

Gases. Most gases are difficult to analyze in biological specimens, because of volatility. Special storage precautions must be taken. Therefore it is advisable to analyze at the poisoning scene or the exhaled vapours by detector tubes, if the nature of the gas is known [1675]. Carbon monoxide is bound to hemoglobin and can therefore be detected in blood [1676,1677,1779,1922,1964]. Methylisocyanate, the Bhopal poison, is another toxic gas (1678,1679). Other gases, such as ethylene oxide and ethylene chlorhydrin [1680], nickel carbonyl [75], which is a very dangerous compound, nitrogen dioxide [1681], ozone [1682], sulfur mustard [1683], nitrite inhalants [1684] and methane [1685] can be monitored. Pharmacokinetic data on gases have been summarized in Table 2.56.

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Normal or asymptomatic range	 Toxic range	Ref.
Acetaldehyde				>0.2	0.9–1.3	75
Aniline		2–7			25	75
	Methemoglobinaemia			0.01–0.5% **	50–80%**	75,1996
Butylnitrite				0.5–4	22	75
	Methemoglobinaemia			0.01–0.5% **	50–80%	75,1996
Camphor					0.3–1.7	75
Coumarine		0.8	1.7	0.02		339
o-Cresol				20–200 (U)	120–190	75
Cyclopropane				anaesth. 80–180		75
p-Dichlorobenzene						
	p-Dichlorophenol					
Fluorocarbons F11				0.5–4.5 *	1.2–32	75
Fluorocarbons F12				0.2–4.7*	0.6–12	75
Fluorocarbons F22					1800–2100	2007
Formaldehyde				0.6–4.0 (W)	1–4,8	75
	Formic Acid			0–12	250–500	75,1997
Hexachlorobenzene		60 days		0.002–0.15	0.2–0.4	75,1998
Hexachlorophene		24		0.003–0.18	24–74	75
Monochloroacetic Acid=MCA					100	1945
Pentachlorophenol		13–19 days	0.35	0.02–0.1 1–20 (W)	>30	28,75
Phenol		0.5		0.1–4.2	46	75
Polybrominated Biphenyls=PBBs				0.001–1.5		75
Polychlorinated Biphenyls=PCBs		7–34 months		0.02–0.03	0.1–2.5	75,1997

***Table 2.55**. Environmental, common chemicals and natural toxicants (continued overleaf)*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Normal or asymptomatic range	 Toxic range	Ref.
Strychnine					0.5–61	75
TCDD (Dioxin)				0.0006 µg/kg (W)		75

(U) = Urine; W = exposed workers. *Therapeutic; **whole blood.

Table 2.55. *Environmental, common chemicals and natural toxicants*

Compounds Parent drug	Main metabolites	Elimination half-time (h)	V_D (l/kg)	Plasma (serum) conc. (mg/l) Normal or asymptomatic range	 Toxic range	Ref.
Carbon Monoxide	COHb	4–5		NS 0.2–2%** S 5–6%**	25–85%	28,75
Ethylene Oxide				0.01–0.1		75
Formaldehyde		1.5			0.6–4.8	75
Hydrocyanic Acid	Formic Acid			0–12	250–500	75,1997
						75
	Cyanide	44–66		NS 0.004** S 0.006**	0.5–50**	75,1434,1467, 2010
	Thiocyanate			NS 1–4** S 3–12**	35–53**	28,337
Methyl Bromide	Inorganic Bromide = Br^-			4–114 (W)	144	75
Methyl Chloride		1–1.5		0.03–0.1 (W)		75
Nickel Carbonyl				0.001–0.005 (as Ni)		75
Phosphine					0.0005	75

(W) = Workers; NS = non smokers; S = smokers. **Whole blood

Table 2.56. *Gases*

INTERPRETATION OF RESULTS

Analytical toxicology includes not only analytical work — with rather complex technical features — but also the interpretation of results. A distinction between types of interpretations is required.

Analytical interpretation

Analytical interpretation is among the most difficult issues in analytical toxicology. Accordingly it requires the greatest expertise from scientific consultants. It also requires a multi-stage process aiming at: (i) verifying laboratory findings; (ii) establishing whether findings are valid by taking into account internal and external quality control (QC) results; (iii) using blind and proficiency-testing specimens; (iv) running a continuous quality assurance programme; (v) determining the significance of the findings, and (vi) accounting for inconsistent results or findings.

This overall process is valid only when the collection and storage of specimens are performed according to state-of-the-art manipulations of the chain of custody. Sometimes DNA analysis may even be necessary [177]. The investigator must have a basic understanding of the performance characteristics of the assays, such as detection limits, accuracy, precision, reproducibility, "cut-off" levels and specificity, use of blanks, spiked samples, correct standards, etc.. Drug metabolites and interfering or cross-reacting substances must be known, as, for instance digoxin-like immunoreactive substances [1715]. The results may not be the last piece in the poisoning puzzle: the laboratory may have stopped at one drug (due to time pressure, lack of specimen, etc.) and another drug may have been overlooked.

The investigator must also be aware of common pitfalls: a patient in a drug treatment centre may introduce other drugs; passive inhalation of cocaine [1709]; drinking coca tea [1836]; interferences in amphetamine immunoassays due to centrally non-active enantiomers of OTC drugs [1710,1923]; presence of the antiparkinsonian drug selegilin [1775,1894] detected by immunoassays and GC-MS; the "poppy-seed defense" story [1711,1712]; the dilution problem [1713], and so on.

Toxicological interpretation

The investigator has to take into account a number of important factors. These are: the dose administered; the frequency of use, the various routes of administration, as the route of administration affects the pharmacokinetics and therefore the detectability in body fluids; the absorption, distribution, metabolism and elimination of drugs [2218], for example amphetamine or methamphetamine produced by metabolism from other substances, such as methamphetamine produced from famprofazone [1714] or from benzphetamine, furfenorex, dimethylamphetamine, selegilin and fencamine, and

amphetamine obtained from fenetylline, ethylamphetamine, clobenzorex, mefenorex, fenproporex, prenylamine, amphetamyl... A good knowledge of clinical pharmacology and toxicology is also essential for understanding, selecting and maintaining assay procedures with adequate detection limits and accuracy, as well as for estimating the duration of drug detectability after use; for taking into account interindividual variations (involving pharmacogenetic factors), impairment estimation (e.g. DUI-cases or similar) [74,76,1600,1828,1849, 1887]; tolerance (100 mg/l phenobarbital in serum is compatible with coma, but may also be a therapeutic concentration for an epileptic patient), and cross-tolerance (prolonged exposure to one drug may result in tolerance to higher doses of a similar drug).

Medical interpretation

The interpretation of toxicological findings by a physician familiar with clinical toxicology or drugs of abuse is more oriented to the patient's personal data including: age, existing pathology (e.g. renal diseases or liver injury); genetic factors (enzyme deficiencies) such as lack of enzymes; tolerance, interactions with other (prescription) drugs or poisons [1830]; "metatoxic" phase of poisoning (the poison is already excreted at the moment the patient is found); interfering factors like heat or cold, stress, fatigue, and bad general health status, which can influence the toxicity of drugs or chemicals.

QUALITY ASSURANCE

A review on analytical toxicology would be incomplete without some comments on quality assurance or quality management. For a number of years (especially with the spread of new analytical laboratories) there has been great concern over the quality of analysis [1716,2180,2181] and the performance of techniques used in various laboratories surveyed [1717–1719,2182,2183]. Proficiency testing is nowadays performed in nearly every country. A considerable amount of experience is available in Spain [1829,2184]. As in other fields of analytical chemistry, the needs for validation of analytical methods, certification and accreditation of laboratories are growing [1721–1723,1999,2000] and guidelines have been established by national authorities or toxicological societies [591,1724–1726,1804,1971,2185,2189]. Proposals to avoid pitfalls were published for example on the use of suitable internal standards [1727–1729], sample storage [1730], avoidance of falsely high concentrations due to contaminated fingers [1731] or laboratory containers. These efforts are not new and papers were published as early as 1969 [1732]. Some authors do not believe this bureaucratic process automatically improves analytical quality [1733] and the future in this field can also be questioned [1734]. Quality assurance can be summarized as follows: write down what you do, and do what you have written down.

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ANNEX: GLOSSARY [3,4,72]

Accuracy = Ability to obtain the real (or true) concentration of an analyte; the degree of accuracy is expressed by the confidence interval of the analytical result.

Analyte = Substance to be identified or measured in body fluids.

Blank = Biological specimen with no detectable drug added, routinely analyzed to ensure that no false-positive results are obtained.

Blind sample = Control material submitted to the analyst (and unknown to him or her) as a routine specimen.

Body packer = Individual who carries drugs wrapped in rubber gloves or condoms in natural cavities of the body.

Chain of custody = Handling samples in a way that supports legal testimony to prove that sample integrity and identification have not been violated, as well as the documentation describing these procedures.

Chromatographic techniques = These are analytical techniques used for the separation of components in a complex mixture based on partition between a stationary phase (e.g. a solid support impregnated with non volatile organic substances) and a mobile phase (e.g. organic solvents) due to selective adsorption at the support's surface. Selective adsorption depends on the chemical structure of compounds to be separated. In thin layer chromatography (TLC), the stationary phase is a layer of a solid support on a glass plate or aluminium sheet. The mobile phase is normally an organic solvent (or a mixture of solvents) sometimes containing inorganic pH-modifiers. After migration (development), separated substances are visualized as spots under UV-light or by chemical reaction. In high performance liquid chromatography (HPLC), analytes are separated under a high pressure of solvents on a small column filled with stationary phase. After separation, substances can be identified in a detector by a method based on retention times and additional spectral properties (UV-VIS, fluorescence, mass spectrometry, etc..). In gas chromatography (GLC or GC), analytes are separated under a flow of a gas (e.g. nitrogen) in a long packed column (1–5 m) or capillary column (15–50 m), and detected by a special detector (ECD, FID, MS...). When suitable reference substances (standards) are available, qualitative and quantitative analysis are possible with appropriate instrumentation.

Coefficient of variation = ratio of standard deviation to absolute value of the arithmetic mean of single analytical values (multiplied by 100) and expressed in %. It gives a measure of repeatability (intra-laboratory) and reproducibility (inter-laboratory).

Confirmation = A second test by an alternative chemical or physical method to positively identify a drug or metabolite. Confirmations are normally carried out on presumptive positives from initial screens.

Cross-reacting substances = In immunoassays, refers to substances that react with antiserum produced specifically for other (related) substances.

Cut-off level (threshold) = The breakpoint (or cut-off point) for labelling a urine result presumptively positive or negative. This level is often provided by the company manufacturing kits. Difficulties in the interpretation of immunoassay results occur when the nature of the analyte is not known. This is particularly so for drugs like

barbiturates or benzodiazepines, where varied cross-reactivities may apply for the various drugs of the group. The consequence may be that a severe poisoning is overlooked by the laboratory.

Detection limit (LOD) = the lowest concentration of a drug that can reliably be detected. LOD = X + 3 s.d., where is X the measured mean background noise of blanks (n > 20).

Diastereoisomers = Pairs of stereoisomers with more than one stereogenic centre which are not related mirror images and have different physical-chemical properties. Optical rotation can differ both in sign and magnitude.

Enantiomers = stereoisomers with non superimposable mirror images. They have identical physical chemical properties, except that they rotate the plane of polarized light in opposite directions by an equal amount.

Extraction techniques = Most toxic substances must be isolated from biological specimens by solvent or CO_2 extraction before they can be analyzed by physical chemical methods in expensive instruments (chromatographs and spectrometers or both combined). Extraction normally requires organic solvents, which are not miscible with water. This generally includes both clean-up and concentration steps. To take into account losses during this extraction and cleanup, the systematic use of a suitable internal standard is recommended.

False negative = Erroneous result in an assay that has indicated the absence of a drug that is actually present.

False positive = Erroneous result in an assay that has indicated the presence of a drug that is actually not present.

Immunoassays = These analytical techniques are based on antigen–antibody reactions. Free and labelled drugs (haptens) compete for limited sites on antibodies in buffered substrate. Drug concentrations can be estimated by the use of markers, namely enzymes, radioisotopes, enzyme substrates, fluorescent compounds, chemiluminescent compounds, when compared to calibrators. Antibodies are obtained from animals treated with the drug to be assayed. There are both homogeneous and heterogeneous assays (including a separation step).

Interfering substances = Substances other than the analyte that give a similar analytical response or alter the analytical result.

Limit of quantification (LOQ) = The lowest measured content (or concentration) above which a quantitative determination of the analyte is possible with specified statistical (un)certainty or degree of accuracy and repeatability.
LOQ = X + 6 s.d.
where X is the measured mean background noise of blanks (n > 20).

Precision = Ability to get the same (quantitative) results between repeated measurements characterized by mean, standard deviation, and coefficient of variation. A distinction is made between "within-day precision" and "day-to-day precision". Inter-laboratory precision is concerned with the measure of reproducibility. Intra-laboratory precision is concerned with the measure of repeatability

Presumptive positive sample = sample which has been flagged as positive by screening, but has not been confirmed by at least an equally sensitive alternative method.

Presumptive tests (initial or screening tests) = First tests carried out on a specimen for determining a presumption of the presence of a substance (or group), later requiring the use of a confirmatory or "second" test.

Proficiency testing = Process of monitoring the capability of laboratories by the provision of previously characterized samples, the characteristics of which are not known to the analyst.

Proficiency testing specimen = A specimen, the expected results of which are unknown to anyone in the laboratory, only to an external agency and later revealed. It is used as an aid to laboratory improvement and conditions of licensing.

Qualitative tests = Chemical tests to confirm the presence of chemicals above minimal concentrations. There is no direct correlation between qualitative screens and clinical effects.

Quality assessment = System for monitoring activities to provide assurance that the quality control activities were performed effectively.

Quality assurance (QA) or management (QM) = Practices that ensure accurate laboratory results.

Quality control (QC) = Techniques used to monitor errors which can cause a deterioration in the quality of laboratory results. Control material most often refers to a specimen (the expected results of which are known to the analyst) that is routinely analyzed to ensure that expected results are obtained.

Quantitative tests = The usefulness of quantitative levels in the management of poisoned patients, impairment estimations, or post-mortem examinations depends on the correlation of drug level to clinical effects. The presence of other drugs, pharmacokinetic variations in overdoses, the formation of active metabolites, individual variations in metabolism including tolerance, and the presence of illness may alter the concentration/effect relationship. Although quantitative tests may not always be required for patients' care, they are very useful for monitoring the quality of analytical techniques.

Reference sample material = Homogeneous, stable material or substance with one or several sufficiently known properties (content) for calibration or confirmation of methods or instrumentation, or the assessment of criteria for the evaluation of analytical results.

Repeatability = Agreement between successive results obtained with the same method on identical test materials, under the same conditions (same laboratory).

Reproducibility = Ability to get similar results in different laboratories under different conditions.

Sensitivity = Measure of the ability of a method to discriminate between small differences in analyte content. Sensitivity is defined by the slope of the calibration curve within the relevant concentration range.

Screening tests = series of initial tests designed to separate samples with drugs at minimal concentration from those below that concentration.

Specificity = Quality of analytical techniques that tends to exclude all substances but the analyte from affecting the result.

Spectroscopic techniques = Analytical techniques based on emission, absorption, fluorescence, phosphorescence and diffraction of different radiations. Mass spectrometry does not use radiation, but it uses electrons to collide with organic molecules in a high vacuum. Under these conditions (normally after chromatographic separations), molecules split into smaller entities. This fragmentation can be used for the characterization of analytes. Atomic absorption spectrometry (AAS), atomic emission spectrometry (AES) and X-ray fluorescence (XRF) are used for detecting and quantitfying inorganic compounds. For AAS, the element to be quantified must be known. AES and XRF can also be used as a screening method for unknown elements.

Validation = Set of measures to ascertain agreement between the performance of an analytical procedure and the requirements of an analytical task.

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3. Risk analysis and toxic substances

INTRODUCTION

In recent years, risk assessment has been a matter of growing interest and concern among toxicologists and health specialists, as well as in the media and among environmental lobbyists [1–5]. Because this is still a relatively new and multidisciplinary field, risk assessment is fragmented, and no general definition is available, hence there is a major limitation to its further development [4].

A critical impetus for the subdiscipline of risk assessment can be found in the growing (even though often biased) awareness of the public and the media, the scientific community and regulatory agencies, that identifying potential toxic hazards is not sufficient, and therefore should be supplemented by assessing, as accurately as possible, the actual risk(s) for human health of exposure to toxic substances. Toxic fears [3] have generated the need for risk analysis. However, as described later in this Chapter, risk analysis should be viewed as a much wider concept than risk assessment.

Risk is usually defined as the chance of injury, damage, or loss, but this definition does not include quantifiable boundaries which are obviously essential when dealing with toxicological issues. Toxic risk is accordingly the chance for adverse (toxic) effects to develop following drug or chemical exposure. Even though taking risk(s) is a part of life, humans are unique in that they ignore high risks taken voluntarily (e.g. car driving or active smoking), but are extremely, not to say irrationally, concerned with small, and seemingly insignificant risks [4].

This chapter is an attempt to define current concepts in risk analysis and to draw a general framework for those toxicologists who are more specifically committed to issues of toxicity in human beings and their societal consequences, such as clinical toxicologists and the staff of Poison Information Centres.

DEFINITIONS

All too often there are no accepted definitions in the fields of risk assessment and risk analysis [4] and each author uses his own definitions in his own

context of concern. This has proved to be a limitation to significant progress in risk assessment and risk analysis, and also a cause for discrepancies or inconsistencies in recently published works, essentially because risk assessment and risk analysis have often been misleadingly used interchangeably.

Hazard

Hazard refers to the ability to cause an adverse effect. As far as chemical substances are concerned, hazard can include flammability, explosivity, radioactivity, causticity, and toxicity [2]. Conventional toxicology has so far been aimed mainly at the identification and, to a lesser extent, understanding of toxic hazards, whatever the source of exposure, whether drug treatment, or environmental or occupational exposure.

Risk

Risk is often used as a synonym of hazard, what it is absolutely not. Risk is actually the probability that some harmful event will occur (interestingly, no one uses the word "risk" when a happy event is expected!) [3]. Therefore, toxic risk is the probability for an adverse outcome following toxic exposure. Uncertainty is a primary component in the definition of risk, as clearly delineated by the National Research Council of the US National Academy of Sciences [6]. Many factors can indeed account for this uncertainty, and a major concern is to distinguish between uncertainty due to lack of knowledge (e.g. unclear mechanisms, insufficient or inappropriate data), and uncertainty due to variability among individuals in a given population [7].

Risk assessment

Risk assessment is the characterization of the potential adverse health effects of human exposure to a chemical hazard, which involves the characterization of the uncertainties inherent in the process of inferring risk [8]. Risk assessment is the process aimed at describing and quantifying the risk(s) associated with exposure to a toxic substance, taking into account data obtained in animals, and possibly in man, the evidence for a dose-effect relationship and/or a threshold dose, and finally data regarding the presumed or actual human exposure. Thus, risk assessment is often classified into four major components: hazard (or toxicity) identification, dose-response evaluation, exposure assessment, and risk characterization [9].

Risk characterization (evaluation or estimation)

It is uncertain whether risk characterization, risk evaluation and risk estimation should properly be used as synonyms, but there is currently no clear difference in their scope. Risk characterization is the process of measuring the

likelihood for a given risk to manifest in the general population or a selected high-risk group of individuals. The information obtained from animal toxicity studies and dose-response evaluation is combined with the information from human exposure evaluation, to produce an estimate of the likelihood of observing the toxic effect in the population under study. Substantial variability exists within any potentially exposed population, and there is also a significant uncertainty in many components of the risk assessment process. It is therefore critical that risk characterization describes the biological and statistical uncertainties inherent to the process in the final estimation, and which component involved the greatest degree of uncertainty. By doing so, it will not only be possible to determine the confidence that can be placed in the final estimation of results, but also to identify the major cause(s) of uncertainty which could be addressed primarily to reduce this uncertainty.

Risk analysis

This is the process encompassing both risk assessment and risk perception. This latter aspect is extremely important as risk management depends totally upon it. Risk analysis is expected to establish methods and criteria that will be useful in assessing the effectiveness of subsequent measures to reduce or control the risk. Thus, it should be viewed as a multidisciplinary field ranging from toxicological to social sciences.

Risk management

This is the process by which regulatory agencies and more generally politicians can evaluate the information derived from risk analysis which is useful for decision making, incorporating political, economic as well as societal considerations. However, because uncertainties are inherent in the risk assessment process, regulatory officials used to include, where appropriate, health specialists (and among them toxicologists) in risk management decisions. This led to the introduction of conservative measures such as safety factors (later called uncertainty factors) [10] to provide the regulator with a greater level of confidence that the actual risk to the human population is very likely to be less than initially estimated. Even though this approach has been justified historically to ensure a prudent public health policy, it nevertheless led to inconsistent levels of protection.

COMPONENTS OF RISK ANALYSIS

Various models have been proposed for the analysis of risk. They generally include at least five components that have been initially separated for a better understanding, but should ultimately be unified in a global perspective of risk analysis. These components are now discussed in turn.

Hazard identification

The very first step in the toxicity assessment of a chemical substance is to establish through the use of animal or in vitro toxicity testing whether it has the potential to cause adverse (toxic) effects in humans [7,8]. It should be stressed that the hazard identification process is primarily qualitative.

The quality of the information provided is based on:

– *The choice of appropriate control groups.* Historical controls are seldom appropriate as techniques evolve markedly as well as the skill of laboratory technicians. The best alternative is the use of randomly selected control animals treated with the vehicle administered via the same route, using the same volume.

– *The use of sufficient numbers of animals.* The larger the number of animals, the greater the power of statistical analysis. However, the number of animals should always be limited to the minimum [11], but heavy pressure from some groups should not result in unrealistic decreases in animal numbers with unreliable toxicity assessment as a consequence.

– *The selection of rigorous experimental protocols.* In the past decades, the scientific excellence of experimental protocols has improved markedly and steadily, and the generalization of good laboratory practices in toxicology centres is a warranty for the rigorous generation of experimental data [11]. However, risk analysis is not restricted to new substances and difficulties arise when it comes to analysing the risk of older substances from data that have been generated in less rigorous experimental conditions.

– *The severity of the effect described.* One of the main objectives of any toxicological evaluation is to determine the target organs of toxicity. The consequences of toxicity depend on the implicit severity of changes observed in laboratory animals following acute or repeated dosing, so that mild changes in clinical biochemistry parameters, for instance, will obviously not be considered as major toxic effects, such as myocardial injury or cancer, would be.

– *The relevance of the mechanism(s) involved.* One major problem is the extrapolation of toxicological findings from animals to man [6,9]. Differences in physiological processes (e.g. hormonal regulation), in susceptibility to a given toxic injury, in the disposition of the toxic substance under study, among other factors, may account for interspecies variations. Thus, even though a major toxic effect is identified in one animal species, it may be explained by the involvement of a specific biotransformation pathway resulting in toxic metabolites that, either do not occur in man, or can be measured at markedly lower levels. Toxicokinetic studies are therefore critically important in studying the relevance of animal findings to man [12]. Another important aspect of hazard identification is the use of mechanistic studies [13]. When a target organ of toxicity is identified, it is important to understand the mechanism of induced changes and to compare the properties of the target site in animals and in man. The evidence for a dose-response relationship is instrumental in predicting whether the expected level of exposure in humans is likely to be associated with target organ toxicity. Finally, the question of whether a threshold exists is of

vital importance for a better assessment of hazard in humans. It is generally held that no threshold exists with carcinogenic substances, so that any low level of exposure could induce cancer. This assumption has obvious consequences for subsequent risk assessment and risk analysis, and is therefore a matter of controversy.

The result of the hazard identification process is a scientific judgement as to whether the chemical can cause toxic effects in humans at some exposure levels [8].

Origin or source of risk

To investigate the origin of risk, a full knowledge of the product formulation is an absolute prerequisite and hence the detailed description of all components included in the formulation as well as the exact percentage of each component in the formulation. Similarly the list of all commercial products which include the substance, the amount manufactured and/or marketed, and the various recommended uses should be clearly known. At the present time, this information is unfortunately not available in many countries and for the majority of chemical substances (except pharmaceutical products and possibly some selected substances). As Poison Information Centres have a key role in the management of acutely poisoned patients, it is recommended that the deposition of detailed information on every formulation marketed in a given country should be legally enforced for this information to be available at any time of the day in such centres. This would also greatly facilitate their growing involvement in the surveillance of chronically intoxicated populations (which is called Toxicovigilance).

The origin of risk should be dealt with through a careful surveillance to store data enabling the detection of relevant changes, for instance, in the amount of product manufactured, consumed, or eliminated within a given period of time, in the actual or recommended modalities of use... Measurements in air, water, food chain, or biological fluids (e.g. the blood and urine of exposed individuals) are helpful to quantify the origin of risk. They will be also helpful to check the usefulness of preventive measures intended to limit or control the risk. However, their value is limited, at least to some extent, by the following factors: firstly, the information gained from these measurements is retrospective (blood or urine levels are obviously indicators of previous and not subsequent exposure) and therefore useless to assess future risk. Secondly, the relevance of selected endpoints may be uncertain or inadequate, as the selection of endpoints greatly depends on the availability of analytical techniques in a given site, and on scientific knowledge at a given time. Finally, the cost of field studies is extremely high.

In some instances, data are obtained in very specific or controlled circumstances, as in the retrospective study or computerized simulation of chemical catastrophes, but the relevance of results from such extreme conditions of exposure is at best unclear.

Human exposure assessment

Human exposure is a major component of risk analysis. Critical information includes knowledge of the duration, magnitude, and route(s) of exposure, and the number and characteristics of the exposed population (e.g. age, gender, occupation, illness). When a pharmaceutical drug [14], or an occupational chemical is concerned, it is often possible to obtain a direct estimation or measurement of exposure. This is no longer so with environmental pollutants, chemical mixtures, or substances present in many household formulations. Biomarkers of exposure, such as DNA or protein adducts, could be useful in this context, but their value has so far not been extensively documented [15]. Mathematical models are therefore often needed to estimate the exposure [16,17] even though no models, whatever their complexity, will ever be able to make up for the lack of data on actual human exposure.

Expected consequences for health

The purpose here is to determine the severity and characteristics of expected health effects in exposed individuals taking into account the composition of the population under scrutiny. Consequences will develop as a number of adverse outcomes, for example death, in the population. Disease registries (e.g. cancer or sentinel events) are especially useful in this context. Expected consequences for health are assessed from available toxicological data [7,8], namely the identification of hazard which relies on the evidence for target organs of toxicity, a dose-dependent response, and the existence or lack of a threshold dose, leading to the determination of a "No Observable Adverse Effect Level" (NOAEL) or "Low Observable Adverse Effect Level" (LOAEL) in animal studies.

Because extrapolation from animals to man is difficult, the use of safety (later called uncertainty) coefficients became widespread [10]. Permissible lifetime exposure levels for humans are calculated using a number of coefficients. Most commonly, they have been extrapolated by dividing NOAELs in animals by ten to account for interindividual variations in susceptibility, and again by ten to account for the uncertain extrapolation from animals to man. Obviously, this is a very conservative approach which is possibly unwarranted [18]: the ratio between NOAELs in rodents and NOAELs in man was found to be ≤ 4 for the environmental chemicals dinitrophenol and carbon disulfide, and ≤ 1 for the pharmaceutical drugs paracetamol, isoniazid, ranitidine, and zidovudine, whereas the above procedure would lead to ultra-conservative ratios.

Ideally, it would be useful to use human data, and in particular epidemiological data [19–21] because man is the species of ultimate interest. However, epidemiological data are seldom available to characterize the expected consequences for health of toxic exposures, due to various limitations. The complexity of phenomena and the involvement of multiple confounding factors are methodological problems which are not easily overcome. The expected toxicity of chemical exposure in humans restricts the use of prospective studies for

ethical reasons. Last but not least the duration of epidemiological studies and the required size of population samples result in extremely high costs.

The experience and database of Poison Information Centres and clinical toxicology departments related to human poisonings, have so far seldom been used for this purpose. This information could nevertheless be very helpful to identify expected health consequences, particularly when no epidemiological data are available, and this should be a strong impetus to the development of a systematic surveillance of the general population, which is called Toxicovigilance.

Risk characterization or risk estimation

This is the final step, the purpose of which is to quantify the risk as well as its likelihood. In practice, it is seldom possible to determine the risk accurately as relevant data are often lacking or inadequate. Therefore, the estimation of risk used to be grossly subjective. Relative estimates are sometimes used to compare a theoretical set of criteria to actual findings [4]. However, this is of no value when the purpose is to decide whether the risk can be accepted or not.

A primary element of risk is uncertainty [22]. Uncertainty that conventional safety (or uncertainty) factors attempted to consider somewhat empirically, is linked to multiple factors that are often associated or combined. They include errors in the measurement of the toxic effect, difficulties due to the retrospective modality of investigations (e.g. measurements in air, water, or biological fluids), problems in the interpretation of data and their extrapolation from animals to man, the empirical value of some findings, and finally, the selection of experimental or mathematical models. Nevertheless, interindividual variability is a critical factor accounting for this uncertainty [23].

Two methods can be used to take into account uncertainty [4]. The conventional method is aimed at defining the likelihood for a given event to occur. As for any risk analysis, the risk alpha will be considered, that is to say the risk for a false positive event to occur, and the risk beta or risk for a false negative event to occur. Another method is based on Bayes' theorem which aims at determining the likelihood for a given event to occur within a given range of likelihood calculated from prior experience or available data.

FINAL ESTIMATION OF RESULTS

Any risk analysis is designed to determine whether the risk can be socially accepted or not, and if not, whether appropriate steps can be taken to curtail or control the risk under consideration. As Kraus et al. [24] put it, human beings have always been intuitive toxicologists. The acceptability of a risk depends highly on the way it is perceived, and the perception of risk was shown to be extremely varied when it is derived from the general public or from experts, or when it is based on socio-cultural, or political considerations, or whatever else [25].

To be accepted, the results of risk analysis should be: (i) logical, that is to say in seeming agreement with theoretical data or the current knowledge at a given time; (ii) extensive, to avoid oversimplification and confounding factors as much as possible; (iii) sensible, to exclude excessive uncertainty, or the view of unreliable experts, and take into account current concerns of the general population.

As a matter of fact, a risk is generally more difficult to accept [4] when it is linked to an unforeseen chemical catastrophe, or when the source (origin) is not familiar or involuntary; when young people or future generations are involved; when risk is a cause for anxiety or helplessness; when it is unequally distributed in the society, linked to poorly valued activities, irreversible or caused by man. The perception of risk is consistently biased, with more or less justified optimism and pessimism [26]. Intuitive judgement has been a hallmark in risk assessment in the recent past [24]: interestingly, it has been shown that large differences do exist not only between toxicologists and lay people, but also between toxicologists working in the industry, the academia or government agencies, and finally it has become evident that toxicologists sharply differ in their beliefs as to whether a chemical's effect on human health can be predicted on the basis of animal studies.

CONCLUSION

Risk analysis is far more than risk assessment based on data obtained during toxicity studies in animals. It should be a rigorous approach encompassing the objective identification of hazard (toxicity), the magnitude and severity of health consequences that are more likely to be observed in exposed humans, the likelihood for these consequences to develop, and finally the acceptation of risk which largely depend on the perception we have.

A rigorous analysis of risk can lead to a sensible and reasonable management based on measures intended to control or curtail the risk under consideration. But whatever its relevance or objectivity, risk analysis is by no means synonymous with decision making.

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4. Acute poisonings in pregnancy

INTRODUCTION

The purpose of this chapter is to discuss the management of acute poisonings during pregnancy rather than the adverse effects of drugs and chemicals upon the pregnant state. Therefore the usually discussed issues of fetal loss, dysmorphology, and adverse effects of therapeutic drug doses in the mother upon the fetus and newborn are not under consideration.

Because there are two patients at risk, acute poisonings during pregnancy present unique challenges. Although the risks in a particular poisoning may not be equal for mother and fetus, treatment is usually quite similar to that delivered to nonpregnant patients because the mother's wellbeing is paramount. However, the presence of the fetus presents two unique management decisions in those poisonings with specific therapy. Should a viable fetus at or near term be emergently delivered for direct delivery of that therapy? Should attempts be made to directly treat a pre-viable fetus in utero? An example of the latter would be cannulation of the umbilical vein in order to inject an antidote that is known not to cross the placenta. While this is an intriguing scenario, it would be a rare circumstance indeed that the human and technological resources required to deliver such therapy could be marshalled quickly enough to have a positive impact.

FETAL AND MATERNAL RISK

For a particular poisoning, the risks to the mother and to the fetus may not be equal. There are many reasons for this. The placenta may act as a barrier to the passage of a potential toxin as in the case of iron [1,2]. Alternatively, the fetal serum concentration could be higher, as has been observed for salicylates [3,4]. Immature fetal metabolic pathways could either increase or decrease fetal risk. An example of the former would be salicylates (persistence of toxic drug) while an example of the latter would be paracetamol (inability to generate toxic metabolite during the first two trimesters). The different fetal homeostatic milieu could contribute to different risks. For example the relative fetal

acidosis decreases plasma protein binding of salicylic acid and increases its penetration into cells. All of the above factors can potentially impact upon the pharmacokinetics and pharmacodynamics of antidotes in the fetus, which could result in relative under or overtreatment of the unborn child. This is of even greater importance when the antidote has agonistic properties. An example of particular concern is atropine therapy in organophosphate poisoning. All of these examples are discussed in further detail in the section on specific poisonings.

EPIDEMIOLOGY

The pattern of overdose during pregnancy by frequency of ingestant is quite similar to that of the nonpregnant adult population with one notable exception — an increased incidence of prenatal supplement ingestion [5]. This is rather unfortunate because the management of iron overdose is difficult enough without having to worry about a fetus.

As in all adult poisonings, the commonest reason for overdose during pregnancy is a suicidal gesture with true accidental intoxications being uncommon [6]. However pregnancy presents other motivations for overdose. These include justification for the procurement of a therapeutic abortion [7] or an actual attempt to induce an abortion [6]. Some agents are commonly believed to be abortifacients. One example is quinine, making its ingestion during pregnancy a strong indicator of that specific intent [8].

Fetal and maternal morbidity and mortality are not particularly high [6]. The ability of the developing organism to withstand toxicological insult may seem somewhat surprising. Also, overdose during pregnancy does not seem to impact negatively upon subsequent reproductive function [9].

MANAGEMENT OF THE PREGNANT OVERDOSE PATIENT

The key principle in the management of the acutely poisoned patient is meticulous supportive care of vital and other body functions [10]. There is very little variance from the management of the nonpregnant patient as the mother's needs are paramount.

Assuming a stable or stabilized patient, attention focuses upon the time honoured treatment principles of the acutely poisoned patient. These are decreasing the absorption of the ingested toxin, increasing its excretion from the blood, and antidotal therapy if indicated. As these issues are described in detail in Chapter 1 of this volume and elsewhere [10], this discussion will be limited to specific issues regarding the pregnant patient and potential effects upon the pregnancy.

The so-called gastric emptying techniques, induced emesis and gastric lavage, have fallen into disfavour with activated charcoal now being considered as

the primary gastric decontamination technique [11–13]. Because charcoal is inert and is not absorbed, adverse effects upon the pregnancy are not expected. In rare circumstances where charcoal would probably be ineffective, such as iron ingestion or the ingestion of modified-release pharmaceuticals which commonly persist for many hours within the intestine and beyond the charcoal's reach, there is another treatment option. This is whole bowel irrigation, the rapid administration of large amounts of specialized lavage solution to irrigate out the contents of the gastrointestinal tract [14,15]. Its use during pregnancy has been described in one patient [16]. Because of negligible fluid or electrolyte flux across the gastrointestinal epithelium, significant impact upon the fetus is not expected.

Increasing excretion is rarely indicated in the treatment of the acutely poisoned patient. In the few exceptions the chief modalities are either hemodialysis or hemoperfusion. The limited published experience indicates that dialysis for acute poisonings does not negatively impact upon the pregnancy [17–19].

Antidotes will be discussed with the specific poisonings. The fetal presence requires ongoing monitoring of its wellbeing, particularly during the acute stage of the poisoning.

SPECIFIC POISONINGS

This discussion will be limited to paracetamol, salicylates, iron, organophosphorous pesticide and carbon monoxide poisonings during pregnancy. The published experience for other poisons is quite anecdotal and is therefore not reviewed.

Paracetamol

Paracetamol is the commonest drug overdose during pregnancy [5] with a large published experience [20–30]. The mechanism of toxic damage is discussed in Chapter 13 and elsewhere [31]. Briefly stated, hepatic damage occurs when the capacity for glucuronidation and sulfation are exceeded, resulting in an increased amount of drug being metabolized by the cytochrome P450 pathway. This generates the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) which is normally bound by glutathione. When this capacity is exhausted unbound NAPQI produces organ damage. N-acetylcysteine is used as an antidote because it acts as a glutathione precursor [32].

Paracetamol freely crosses the placenta thus the fetus is at risk [33]. Estimation of risk requires knowledge of the capacities for glucuronidation, sulfation, P450 activity and glutathione stores. Glucuronidation is essentially absent throughout gestation and remains low in the early newborn period whereas sulfation is quite active during fetal life [34,35]. Therefore, in the fetus, a relatively increased amount of paracetamol is available to the cytochrome P450 pathway. It is the activity of the latter that is the chief determi-

nant of fetal risk. It turns out that this system is only at 10% of adult activity at the midpoint of gestation, with activity increasing with gestational age [36]. Therefore risk is expected during the latter part of pregnancy. Since NAPQI is generated and remains intracellularly, fetal risk would be expected only during the third trimester. This is supported by the observation that published fetal deaths due to maternal paracetamol overdose have been third trimester events [20,28].

Treatment of paracetamol poisoning in pregnancy should follow that recommended for the nonpregnant population (see Chapter 13). N-acetylcysteine is the antidote of choice. There are intravenous and oral protocols for its administration. As the parenteral formulation is not licensed in America, the oral protocol is chiefly used there. The relative merits of these routes of administration have been debated for more than a decade. However this may be a moot argument for the fetus because of recent animal evidence demonstrating very poor passage of N-acetylcysteine across the placenta [37]. Thus it would seem to be more sensible to treat the pregnant paracetamol overdose patient intravenously since this results in higher maternal antidotal serum concentrations.

If the pregnancy is at or near term, consideration should be given to emergent delivery in order to directly administer the antidote to the newborn, particularly in cases with very high serum paracetamol concentrations. Fortunately, the pre-viable fetus is at decreased risk for paracetamol hepatotoxicity because of its relative inability to generate toxic metabolite.

Although teratogenicity should not be a reason to withhold an antidote in a mother with a life-threatening poisoning, it is comforting to know that N-acetylcysteine does not appear to be teratogenic [20,21].

Iron

Iron poisoning is discussed in Chapter 17 and elsewhere [38]. It is the second most common overdose during pregnancy in North America [5] and several cases have been reported [39–45]. Of particular interest is that the risk seems to be relatively less for the fetus.

The decreased risk for the fetus is a consequence of the mechanism for transplacental iron transport. It is an active saturable process that shields the fetus from maternal hyperferremia [1,2]. Supporting evidence has been produced in an iron overdose model [46]. Massive maternal hyperferremia induced by intravenous iron injection resulted in negligible increases in simultaneously collected fetal serum specimens. Case reports of normal neonates emergently delivered from fatally ill iron poisoned mothers also support the concept of relative decreased risk for the fetus [44,45]. Although shielded from maternal hyperferremia, the fetus is potentially at risk secondary to the maternal physiologic derangements which would be the usual cause for the need for emergent delivery.

Ingestion of more than 1.5 g of elemental iron by an adult is a cause of concern, with management being no different than for a nonpregnant patient

[38]. Unique management features of iron overdose include the importance of abdominal X-rays in verifying and quantifying ingestion and the role of whole bowel irrigation as a primary gastrointestinal decontamination procedure. Chief concerns for the mother are shock, acidosis and hepatotoxicity. Meticulous supportive care, often in a critical care setting, is essential for the management of this poisoning.

There are many uncertainties regarding the optimal use of deferoxamine, the specific iron chelator. These include indications, dose, route, and duration of therapy. Compounded upon this are concerns regarding potential teratogenicity, with the manufacturer specifically cautioning against its use during pregnancy. These concerns are based upon skeletal abnormalities observed in laboratory animals receiving chronic deferoxamine during early stages of pregnancy [42,47] (a model intended to simulate the treatment of chronic iron overload). It is likely that the skeletal anomalies were a consequence of chelation of minerals essential for skeletogenesis. Case reports of women with chronic iron overload conceiving and carrying a pregnancy with a normal outcome while receiving continuous deferoxamine therapy [47,48], and the limited described experience of treatment of acute iron poisoning during pregnancy with this chelator without evidence of teratogenicity [39], are reassuring. Withholding an indicated antidote because of teratogenic concerns is not rational because the mother's wellbeing is of primary concern. Therefore the indications, dose, route of administration, and duration of deferoxamine treatment are the same for pregnant and non-pregnant patients (see Chapter 17).

Salicylates

Salicylate poisoning has become less common, with its replacement by paracetamol as the most prevalent antipyretic/analgesic. From the acute overdose perspective, this is a positive occurrence because of the former's greater degree of toxicity. In contrast to the situation with iron, the fetus seems to be at greater risk than the mother. Of the three reports of acute salicylate overdose during pregnancy there were two fetal and no maternal deaths [49–51].

There are several reasons for this increased fetal risk. Plasma salicylate concentration is higher in the fetal side of the placenta [3,4]. Fetal metabolic pathways are immature and are less able to metabolize the salicylate load. Also the fetus has a smaller buffering capacity, making it less able to cope with salicylate induced acidemia. The lower arterial pH in the fetus favours increased salicylate cell penetration because of the smaller intracellular to extracellular pH gradient and decreased plasma protein binding.

Treatment should be no different than for the non pregnant patient. It is described in Chapter 13 and elsewhere [52]. Because of the increased fetal risk, early consideration should be given to the delivery of the mature fetus for direct provision of supportive care in situations of significant maternal salicylate intoxication.

Organophosphorus pesticides

Acute organophosphorus pesticide poisoning during pregnancy is not common; however there are several case reports [53–56]. The fetal presence complicates management because of differing sensitivities to the poison and because its antidote, atropine, is a potent agonist. Organophosphates cross the placenta [54]. Because there are many of them, it is reasonable to expect that fetal penetrance differs from compound to compound. Of greater importance however, is that the target organ in the mother is her lung, which is not a vital organ in the fetus. A further complicating factor is that the fetus has 50–70% less cholinesterase activity than its mother [57–59]. Therefore a therapeutic maternal atropine dose could be either toxic or subtherapeutic for the fetus.

The basic management of organophosphorus insecticide poisoning during pregnancy should not differ from that of the nonpregnant patient (see Chapter 20). This includes meticulous support of respiratory function and the provision of atropine [60]. However, close monitoring of fetal wellbeing is critical because of the above factors. If distress is observed in a mature fetus, then consideration should be given to emergent delivery in order to care directly for the baby.

Carbon monoxide

Carbon monoxide poisoning is described in detail in Chapter 26 and elsewhere [61]. It binds to hemoglobin and thus decreases the oxygen carrying capacity of the blood placing the patient at risk for hypoxic damage. A fetus is at greater risk than its mother because of the higher affinity of fetal hemoglobin for carbon monoxide and because of the longer elimination half-life in the fetus [62]. Also, because the fetal oxyhemoglobin dissociation curve is shifted to the left and the pO_2 is normally lower, a small decrease in oxygen tension causes a relatively larger degree of hypoxia in the fetus [63]. Clinical experience has demonstrated a relative increase of risk for the fetus with many examples of fetal morbidity and mortality with less severe maternal outcomes [64,65].

Hyperoxia has long been the mainstay of the treatment of carbon monoxide poisoning with hyperbaric oxygen often recommended as the treatment of choice. Because of the increased fetal risk the argument for hyperbaric oxygen therapy during pregnancy is even stronger. It has been calculated that in order to clear the fetus of carbon monoxide with normobaric 100% oxygen, one would need to continue its administration to the mother five times as long as it took to normalize her carboxyhemoglobin concentration [66].

Hyperbaric oxygen therapy presents theoretic risks for the fetus. These include teratogenicity, retinopathy of prematurity and premature closure of the ductus arteriosus [63]. However, clinical experience to date has not resulted in confirmation of these potential adverse effects [64,67]. Therefore if facilities are available, it would seem that hyperbaric oxygen therapy should be used for carbon monoxide poisoning during pregnancy. Indications include symptomatic mothers, fetal distress, or a maternal carboxyhemoglobin concentration greater than 25%.

Miscellaneous poisonings

There are many anecdotal reports of various poisonings during pregnancy. Data are insufficient for meaningful review. For interest, they are listed in Table 4.1.

Poisoning	Ref.
Amanita phalloides	68
Arsenic	69,70
Camphor	71–74
Ciguatera	75,76
Digitalis	77
Lead	78–85
Naphthalene	86,87
Nutmeg	88
Paraquat	89–91
Quinine	8
Snakebite	92

Table 4.1. *Miscellaneous poisonings in pregnancy*

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5. Food and drug additives: hypersensitivity and intolerance

INTRODUCTION

A number of substances, known as additives, are authorized for use by the industry for technological purposes in the manufacture of foods or drugs. Due to critical changes in modern nutritional habits, there has been a considerable diversification of additives together with the increased use of new or processed proteins [1]. From 1500 to 3000 chemical substances are added to the food supply as direct and secondary additives [2]. Routinely used direct additives include colouring agents, preservatives, antioxidants, stabilizers, jellifiers, binders and thickeners, flavouring agents, taste enhancers and sweeteners. Yeasts and enzymes are also used in the manufacture of various foods. Finally, a wide number of manufacturing aids are used for hydrogenation catalysis, cooling by contact, extraction by solvents, lubrification, or as propulsive agents, resin ion exchangers, plucking or unmolding agents [2,3].

More or less stringent standards are applied to the use of food additives. Acceptable daily intake (ADI) is set by the JECFA (a joint FAO/WHO committee) for most additives, but some, such as natural flavouring agents, are not considered. In addition, considerable interindividual variations in daily intake due to nutritional habits are a major source of concern which, again, is not addressed by the regulations in force to maintain the safety of authorized food additives.

The chemical nature of food additives is varied. It includes low-molecular-weight haptens, polysaccharides, complex fats (e.g. lecithins), small peptides or proteins. In addition, additives such as sucrose polyesters [1] were recently introduced. Additives, strictly speaking, may be contaminated by an impurity during the manufacturing process. They may also interact and form new compounds. Another specificity of food additives is the wide variability of ingested doses, from less than 1 mg (most haptens) to over 10 g (e.g. polysaccharide gums). It is therefore reasonable to assume that adverse reactions to food additives may involve many different mechanisms.

The overall health risk related to additives has been incompletely evaluated. They were suggested to cause 0.1% of allergic reactions in Denmark [4]. An

EEC working group estimated the incidence between 0.03% and 0.5% [5] and a study performed in 1987 in United Kingdom found an incidence of 0.026% [6]. As a matter of fact, the incidence is certainly much higher in the 1990s. Since the first paper by Michaelsson and Juhlin [7], the role of tartrazine and benzoate has been minimized, but that of metabisulfites has been recognized whereas the allergic risk involving flavouring agents, plant gums and new proteins remains to be evaluated. Thus, intolerance to metabisulfites in patients with asthma was not well recognized before 1980 [8]. Nevertheless, the incidence of asthma is increasing and 5% of the population is currently affected. Similarly, sensitization to natural flavouring agents and to synthetic agents identical to natural substances appears to be widespread in children with atopic dermatitis who account for 5% of pediatric patients.

CLINICAL ASPECTS

Clinical presentation

Chronic urticaria, angioedema and asthma are the most frequent clinical signs. Various skin reactions, fever, vasomotor rhinitis, purpura with cutaneous vasculitis, oral aphthous ulcerations, recurring cheilitis, contact dermatitis (of occupational origin in most instances) and myositis have all been described [7,9–20]. The role of allergy to food additives in small children with atopic dermatitis has also been stressed [21]. Fatal outcomes, as a result of shock or acute asthma, have been reported only in the case of metabisulfites [22,23].

Psychological and neurosensory complaints, namely asthenia, depression, irritability, psychomotor agitation, difficulty in intellectual concentration, loss of memory, headache, have been reported in some patients and these complaints have been largely publicized by the media. In particular, azo colouring agents have been incriminated and Feingold coined the term "hyperactive child syndrome" [24]. Without denying the reality of these symptoms [25], it should be stressed that when associated with organic disturbances (e.g. diarrhea with abdominal pain) they may actually be related to the psychological impact of chronic illness [26]. By contrast, when isolated, they usually could not be reproduced by challenge tests conducted according to a strict methodology. These symptoms are often noted in subjects with a specific psychiatric profile and such case reports may justifiably be classified under the heading of food-related neurosis.

Risk factors

The question whether some factors facilitate or precipitate food intolerance or allergy must be raised. With respect to food additives, four groups of patients seemingly at a greater risk for adverse reactions can be identified clinically:

The first group includes patients with asthma, most often of intrinsic type and often associated to naso-sinusal polyposis and intolerance to aspirin, nonsteroidal anti-inflammatory drugs, glafenin, codein and, in rare instances, paracetamol. This disorder was described by Fernand Widal in 1922, and is also known as Samter's triad. Challenge tests to suspected additives were found to be positive in 16% of these patients (Table 5.1). The following additives metabisulfites, benzoic acid, tartrazine and menthol have been incriminated [27,29]. Metabisulfite intolerance was reportedly involved in about 8% of corticosteroid-dependent asthmatic patients who appeared to be most at risk [28]. Sodium benzoate was found to elicit bronchospastic reactions in three studies [30,32]. Intolerance to tartrazine has been claimed to be frequent [31]. However studies using double blind placebo controls show that intolerance to tartrazine is undoubtedly unusual and does not exceed 2% to 3.5% of patients with asthma [27–32].

Additives	n	Negative	Positive
Tartrazine	21	19	2
Sodium benzoate	17	15	2
Sodium metabisulfite	5	2	3
Total	43	36	7 (16%)

(Tartrazine and sodium benzoate have been systematically tested. Sodium metabisulfite has been tested when the case history revealed intolerance to alcohol. The criterion for a positive response is a fall of at least 15% in peak expiratory flow within 2 hours of ingestion of these substances.)

Table 5.1. *Oral provocation tests to food additives in 34 patients with Fernand–Widal Syndrome (Samter's triad)*

The second group includes patients with chronic urticaria or atopic dermatitis. In extensive studies, oral challenge tests were positive in 5–10% of cases. Several additives are usually detected in a single patient [7,12,21,33,34]. Apart from azoic dyes and benzoates, BHA and BHT have been recently reported [35]. The high rate of positive reactions to placebos, as well as the variable results obtained from elimination diets, explain why the incidence of intolerance to additives in patients with chronic urticaria continues to be elusive.

The third group includes patients with an allergy to food protein allergens [36]. For instance, oral challenge tests with additives were positive in 26% of 150 patients with food allergy (Table 5.2).

The fourth group includes occupational allergies in workers of the food industry and restaurants: skin (contact dermatitis) or respiratory (rhinitis and asthma) allergy are commonly ascribed to BHT, BHA, alpha-amylase, cochineal red, etc. [11,37,38]. Daily exposure to the offending additive is the major risk factor in these patients.

Additives	n	Negative	positive
Sodium nitrite	15	13	5
Sodium benzoate	5	4	
BHT	4	4	
Tartrazine	9	6	3
Amaranth red	11	8	3
Erythrosine	4	2	2
Sunset Yellow (FD&C Yellow No. 5)	4	4	0
Scarlet red	f3	1	2
Total	55	38	14 (16%)

(Tests were performed with additives chosen based on the results of a food investigation conducted for a week. Food additives ingested twice a week or more were tested in capsule form given by oral route. Positive results were urticaria developing within no longer than two hours.)

Table 5.2. *Oral challenge tests to food additives in 150 patients with immediate type food allergy*

With respect to drug additives, the risk for adverse reactions (generally involving a hypersensitivity mechanism) is apparently not related to a particular context but rather to the repeated use of the additive. Ointments and eyedrops predispose to the development of delayed hypersensitivity reactions following contact with the additive, and manifest primarily by eczema [11]. Additives in drugs for parenteral administration carry a higher risk for anaphylactic shock.

MECHANISMS OF ADVERSE REACTIONS

The mechanisms of adverse reactions are classified in two major categories: immunological and non-immunological.

Immunological mechanisms

Immunotoxicity covers all adverse effects on the immune system: effects on organs (especially the thymus and the Peyer's patches) and effects on cells, i.e. immunocompetent cells (macrophages, lymphocytes and plasmocytes), and effector cells (mast cells, basophils, eosinophils, neutrophils, platelets and other target cells) [39–41]. Generally speaking, immunotoxicity caused by food additives is still very poorly understood: very few epidemiological studies have been conducted and methods were inaccurate. Lastly, there is no strategy for prevention using animal testing predictive of additives immunotoxicity prior to approval for use in humans. Reactions related to immunotoxicity can be classified into four different groups: hypersensitivity, pseudoallergy, autoimmunity and dysimmunity.

Hypersensitivity to additives has been documented by a number of case reports. The sensitizing antigen can be a protein (e.g. alpha-amylase, natural vanilla or papain) or a hapten coupled to a protein [39,42]. The hapten is the parent molecule or a metabolite. There are many routes for sensitization: digestive (ingestion), nasal and bronchial (inhalation), cutaneous and ocular (direct or airborne contact). Conditions for sensitization are also varied. Sensitization via ingestion of the antigen is the commonest. Occupational-related sensitization occurs especially by inhalation, and proteins, such as enzymes used during the manufacturing process, carry a high risk for occupational asthma [37,43]. Sensitization may also be caused by a drug formulation containing the additive or by a cross-reacting environmental chemical, as evidenced by the cross-sensitization between the textile dye yellow no. 11 and the food colouring agent quinoline yellow (E104) [9,44].

Two types of hypersensitivity reactions are the commonest. According to Gell and Coombs, type I is characterized by specific IgE which bind to tissue mast cells and circulating basophils. Upon subsequent contact with the antigen, sensitized cells release chemical mediators, in particular histamine, hence resulting in anaphylactic shock, asthma, cutaneous eruption, acute abdominal symptoms, purpura, etc. Type IV involves sensitized T lymphocytes. When activated by an allergen, they release cytokines and produce cellular infiltrates resulting in organic disorders of which contact dermatitis due to food additives is a typical example.

Prediction of the sensitizing potential of additives is possible using various techniques [42,45,46] but is not done at the present time even though a number of additives have been shown to induce hypersensitivity reactions.

(1) *Colouring agents*. Since the first report by Lockey [47], the risk for sensitization to colouring agents, particularly azo dyes, triphemylmethane derivatives and the natural substance annato, has been well identified [48–50]. Latent sensitization without clinical reaction after ingestion of the antigen, and anaphylactic shock at the time of the first injection, can occur as evidenced by patent blue [49]. This dye is injected on the dorsal part of the foot to visualize the lymphatic vessels. Specific IgE to cochineal red have been highlighted [38]. Photosensitization has also been reported with sunset yellow and erythrosine. The mechanism of hypersensitivity in leukocytoclastic vasculitis has not been clearly established [13,50].

(2) *Food preservatives and anti-oxidants*. These agents used in food preparation mainly include aliphatic acids (which are always harmless), mineral compounds and aromatic acids. They very rarely cause sensitization: a few cases of eczema, asthma or urticaria related to butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA) have been reported [35,46,51]. Similarly, polymorphous erythema has been related to a true hypersensitivity reaction to benzoic acid [52]. Sorbic acid, both a food and drug preservative, has a very slight sensitizing potential [52,54] and the same is true of propylene glycol [51,55]. The safety of lecithins has recently been debated [56]. Sufficient data on residual protein concentrations are not available, although this is a key

issue for the allergologist when egg or soybean lecithins are involved. Whether repeated ingestion is truly safe in subjects extremely sensitive to these proteins is debatable. It is beyond doubt that metabisulfites are the most harmful preservatives in high-risk patients, such as asthmatics [57]. Metabisulfites cause acute bronchospasm by a vagal reflex. However, a few case reports of systemic reactions, for instance skin eruptions with fever or shock, with positive skin tests and histamine-release from leukocytes, confirmed that a hypersensitivity mechanism is likely to be involved [10,58]. In addition, metabisulfites in food could result in asthma with continuing dyspnea in intolerant patients. Found in sizable amounts in wines and alcohols, in some prepared foods and dried fruits, metabisulfites have been blamed for "restaurant anaphylaxis" [10].

(3) *Sweeteners*. Saccharin (sodium benzoic sulfimide) is a sensitizing substance as evidenced by specific IgE, lymphocyte sensitization or photosensitization. A possible cross-reaction with sulfonamides has also been described [59]. Aspartame which consists of aspartic acid and phenylalanine should not be ingested by patients with phenylketonuria. Phenylalanine serum levels are significantly higher in healthy heterozygotes than normal subjects. The consequence of this finding is unknown. Beside the possible adverse effects of high doses of aspartic acid on the central nervous system, the formation of a diketopiperazine derivative must also be taken into account as it is believed to be sensitizing, and to induce the synthesis of specific IgE resulting in recurrent urticaria, although this is seemingly very uncommon [60].

(4) *Texturing agents*. Binders, stabilizers, thickeners and jellifiers are seldom involved in hypersensitivity reactions. However, angioedema and anaphylaxis have been reported with tragacanth or arabic gum [61]. The immunogenicity of these high-molecular-weight polysaccharides has been suggested to be related to residual proteins [62,63]. Sensitization to several gums has been evidenced by skin tests in patients with clear susceptibility to vegetables (e.g. soybeans and peas). In fact, arabic gum, tragacanth and locust-tree gums belong to the same plant family. More frequent allergy to gums has been reported since 1991, a finding which may be related to their recent widespread use by the food industry. Their use as colour-dispersing agents and in alcoholic beverages as well may be a matter of concern as alcohol can alter intestinal absorption. Possible occupationally-related asthma or contact dermatitis due to vegetable gums and to carobban have recently been reported [64–66].

(5) *Flavouring agents*. These additives are currently the focus of attention. A variety of chemical entities are involved including natural flavouring agents, synthetic agents identical to natural agents, and artificial agents. The exact composition of flavouring agents is either unknown or, if known, patent-protected. There is no ADI for natural flavouring agents and the concentration recommended in finished products encompasses an unknown margin of variation. There are no letter codes. Flavouring agents (natural, artificial) as listed on food product labels actually provide very vague information to the allergologist. Moreover, dietary habits dramatically changed during the last two years so that flavouring agents are increasingly added to food products (Table 5.3).

Case	n	Natural vanilla	Vanillin	Natural flavourings(1)	Artificial flavourings(2)
1	4	12	7	–	
2	1	–	28	–	
3	19	3	–		14
4	4	–	41	4	
5	5	26	2	–	
6*	6	3	2	–	
7	–	9	–	–	
8	3	7	1	–	
9	3	23	–	–	
10	–	21	–	1	
11	9	–	3	15	
12	3	4	8	6	

6*: 69 doses of azo coloring agents per week;
(1) may contain vanillin;
(2) may contain methylvanillin.
Results are presented as number of doses per week.

Table 5.3. *Weekly consumption in 12 children with atopic dermatitis (Moneret-Vautrin, 1991)*

n	Sex	Age	Placebo	Peru	Vanilla	Vanillin
1	F	3.5 yr	2:–	–		
2	F	2.5 yr	1:–	+		
3	M	12 mo	1:–	+		
4	F	2.5 yr	1:–	++		
5	M	10 mo	1:–	+		
7	F	3.5 yr	2:–		–	–
9	M	12 mo	1:–		++	++
10	F	2.5 yr	1:–	+	nd	+
11	M	10 mo	4:2	+	+	:2±
12	M	5 yr	1:–		–	+

Substances tested at a 3 day interval in capsule form taken by mouth using double-blind design. A positive result consisted of development of a rash exacerbating atopic dermatitis, 12 to 48 hours after ingestion of the substances.

Table 5.4. *Double-blind oral challenge test in 12 children with atopic dermatitis (results from Moneret-Vautrin)*

We showed that young children (under 5 years of age) with atopic dermatitis were sensitized to vanilla and vanillin (Table 5.4). Delayed hypersensitivity was likely in the majority of cases because of the delayed reaction following oral challenge and the clinical presentation which was marked by worsening of eczema [67].

(6) *Manufacturing aids*. Their possible role in hypersensitivity reactions is seldom considered. Several enzymes added to flour are likely sensitizers and co-allergens responsible for baker's asthma. Alpha-amylase extracted from the fungus *Aspergillus orizae* is an extremely sensitizing flour additive: 24% of bakers with occupational wheat flour-related asthma were found to be co-sensitized to this allergen [43]. As it is likely to be destroyed by cooking, no adverse effects should be expected following ingestion [68]. However a single observation suggests possible food induced reactions, as an oral challenge to alpha-amylase was able to provoke asthma in a sensitized worker [69].

Other enzymes, for example alpha-amylase from *Bacillus licheniformis*, hemicellulase from *Aspergillus niger*, protease from *Bacillus subtilis*, a soybean lipooxygenase and papain are less commonly involved [43]. 2.5% baker's yeast (*Saccharomyces minor*) is incorporated in baking dough and the sensitizing potential is retained after cooking. Incorporation of such yeasts in home-made pastries, as well as dietetic foods and drugs, the so-called "food health products", involves a particular risk. The beer-clarifying agent papain is also used as a bakery additive, and is found in toothpastes, pharmaceutical drugs and fruits (papaya). Latent sensitization was found in 1% of the US population [70]. The risk for anaphylactic shock is well-known. It may be fatal when papain is injected during chemonucleolysis. Anaphylaxis after drinking beer has been described [71]. In all cases, specific IgE have been demonstrated and RAST for some enzymes are also available.

(7) *Food proteins*. New food technology is expanding the use of food proteins because of interesting characteristics. The egg-white extract lysozyme used as a bactericidal preserving agent in some foods, most commonly of plant origin, can be considered as an additive. Lysozyme was found in about fifty different foods in Japan at concentrations up to 1 mg/100 g [72]. Its use at higher concentrations in various kinds of cheese is under consideration by the JECFA [73]. The lack of label information indicating the presence of lysozyme is a definite risk for serious adverse reactions in patients allergic to eggs, as lysozyme is a common allergen in egg-white [74]. Similarly, the marketing of Simplesse® in several EEC countries, Japan and Australia, is focusing attention. This product is a mixture of lactoserum and egg proteins. In the manufacturing process, the proteins are altered to microparticles 0.1 to 3 μm in diameter. Simplesse® is used in many cream-based desserts, mayonnaises and salad dressings as a replacement for fat. It may account for up to 40% of proteins present. As the allergenicity of milk and egg proteins was found to be unchanged, there is a risk for patients allergic to cow's milk or eggs [75].

(8) *Pharmaceutical additives*. The direct inhalation of metabisulfites in beta-stimulant aerosol sprays [76] is no longer possible as these formulations have been withdrawn from the market. Drug formulations for injection (especially intravenous) including metabisulfites (e.g. doxycycline, aminoglycosides, local anesthetics with epinephrine, several corticosteroids, etc.) still pose a major risk. Rectal formulations have been incriminated [18,77].

Cremophor El®, a polyoxyethylene castor oil derivative, included in vitamin

K and cyclosporin preparations and in Althesin®, an anesthetic agent withdrawn from the market, proved to cause anaphylactoid shock [78,89].

Merthiolate induces a high incidence of latent sensitization [80], in particular in health-care staff who are vaccinated frequently and exposed to merthiolate-containing antiseptics [81]. In addition to ocular allergic reactions to eyedrops, acute laryngeal edema secondary to localized spray administration [82], systemic reactions following vaccination [83] and anaphylactic shock following the injection of merthiolate-containing heparin formulation have been described [84]. Merthiolate can also be found in immunoglobulin preparations.

Formaldehyde is commonly found in vaccines and in many toothpastes. Latent, delayed-onset sensitization is relatively common and can be observed in 4–6% of patients with eczema. The incidence is reportedly much higher in health-care staff possibly because of hepatitis B vaccination [85]. Exposure to formaldehyde is also frequent during hemodialysis, and eczema in hemodialysis patients is often due to formaldehyde [86]. Its common use in toothpastes has caused outbreaks of eczematous cheilitis. More worrisome is acute angioedema following dental treatment with formaldehyde-containing obturating material: high levels of specific IgE were found in one patient [87]. Another case of anaphylactic shock has been reported in a patient undergoing hemodialysis [88].

A few cases of eczematous dermatitis following injection of chlorocresol [89] or chlorbutol [90] have been reported. Myositis with myalgia and elevated creatinine phosphokinase was associated with m-cresol, used as a preservative in a growth hormone preparation [19]. A systemic hypersensitivity reaction has been observed following injection of benzyl alcohol [91]. Similarly, parabens (common preservatives in ointments and also in local anesthetics) caused urticaria or eczema [92–94] and rarely asthma [95]. As these were often early reports, it may be hypothesized that cross-reaction in subjects sensitized to procaine, a very sensitizing drug commonly used in the past, was actually involved. The incidence of paraben-induced chronic dermatitis is about 1% [51]. Systemic reactions are very rare [96].

Polyvinylpyrolidone is used in foods and to date no adverse events have been reported. By contrast, when used in drug formulations, allergic vasculitis following local application [97] and anaphylactic shock after injection of an iodinated contrast agent [98] have been reported. Carboxymethylcellulose (CMC) caused contact dermatitis [99] and IgE-dependent anaphylaxis [100], in particular following the injection of corticosteroids [101–104]. Its increasing use by the food industry deserves further attention [104]. Although no allergy to CMC as a food additive has been reported until now, the risk in patients with a history of anaphylaxis to CMC in injectable sustained-action corticosteroids is unknown.

Pseudoallergic reactions derive from the ability of various substances to induce clinical reactions mimicking allergy, such as urticaria, angioedema, asthma, and anaphylactoid shock, through non-specific release of chemical

mediators [27,36,46,105]. Along with other authors, we are militantly advocating this strict definition in contrast to some English-speaking authors who tend to call pseudoallergic reactions any such reactions with a psychiatric context.

(1) *The non-specific activation of complement* has been alleged for Cremophor El®, judged to be the culprit of anaphylactoid reactions to Althesin® [106].

(2) *Non-specific histamine release* could account for several observations of reactions to Cremophor El®, according to the histamine releasing effect which has been demonstrated in dogs [107]. Similarly, various local or systemic reactions following injection of a drug formulation containing propylene glycol as the solvent might involve non-specific histamine release, because of the hyperosmolarity caused by propylene glycol [109].

(3) *The non-specific release of arachidonic acid by-products* may be involved in reactions to benzoic acid, high doses of metabisulfites, azo coloring agents, and menthol, in patients with intrinsic asthma, naso-sinusal polyposis, chronic urticaria [16,29,109,110]. Patients exquisitely reactive to low doses of aspirin and nonsteroidal anti-inflammatory agents are most at risk in developing intolerance to the above-mentioned additives [16,29]. In addition, in patients intolerant to these additives following oral ingestion, the intravenous injection (as in drug formulations) may be life-threatening [16]. It is assumed that these additives might interfere with the metabolism of arachidonic acid, leading to the release of prostaglandins, leucotrienes and free radicals from oxygen. A recent study confirmed the abnormal release of prostaglandin 6-keto PGF alpha and histamine from the gastric mucosa in the presence of benzoate, in patients with a positive oral challenge test [111]. A state of activation of different kinds of cells (eosinophils, macrophages, mast cells, etc.) has been demonstrated in asthma, nasal polyposis, and atopic dermatitis. These activated cells are prone to release derivatives from arachidonic acid, in various conditions.

(4) *Non-specific activation of lymphocytes and cytokine release*. Experimental results with the heavy metals, gold, nickel, and chromium, suggested this mechanism is likely to be involved. To date, it has not been reported with additives.

Autoimmunity has been proposed as the possible mechanism of the Spanish toxic oil syndrome. A complex substance, namely an isothiocyanate residue produced by heating of an aniline derivative and subsequently bound to denatured fats, has been suggested to be involved. The clinical presentation was compared to graft-versus-host disease [112].

More recently, an autoimmune mechanism has been proposed for the eosinophilia-myalgia (EM) syndrome, identified as a separate clinical entity affecting over 1500 patients in the USA [113,114]. This syndrome combines myalgias, arthralgias, cutaneous eruptions with edema of the extremities and periorbital edema, eosinophilia, slight fever and laboratory evidence of inflammatory syndrome. Complications of the disease include pulmonary and nervous manifestations which accounted for 27 reported deaths. The causative agent is a dietary agent (or drug product) L-tryptophan. Interestingly, the

majority of severe adverse reactions occurred with a Japanese brand of L-tryptophan and component E, resulting from the indolization of 2 L-tryptophan molecules, was identified as the contaminant possibly involved. The ingested dose was highly variable and sometimes minimal [114]. There is a striking similarity with the clinical and laboratory features of Shulman's eosinophilic fasciitis which has been suggested to correspond to undiagnosed cases of EM. Several clinical signs (multiple organ involvement, similarity with Schulman's syndrome, sclerodermiform symptoms) are suggestive of an autoimmune disease. The hypothesis that still unidentified substances in food, may cause unclassified autoimmune disorders with multiple organ involvement should therefore certainly be taken into consideration.

Dysimmunity is the term proposed to characterize granulomatous disorders and consequences of acquired immunosuppression. One study incriminated cinamaldehyde and azo colouring agents in cases of oral-facial granulomatosis with persistent edema of the perilabial area associated with histological abnormalities involving granulomas in a cellular infiltrate [115]. Immunosuppression has been experimentally documented for a variety of chemicals: heavy metals, aromatic hydrocarbons, halogenated or aromatic compounds, etc. There is a paucity of research with BHA [40].

Two epidemiological studies investigated the incidence of respiratory infections related to depression of cellular immunity in populations exposed to food contaminants (aromatic and halogenated compounds in drinking water and dairy products). Immunosuppression can coexist with auto-antibodies. Recurrent infections have been observed [116–118]. To our knowledge, no other similar study implicating food additives has been reported [39,40].

Non-immunological mechanisms

Interference with neurotransmission may occur in the central or peripheral nervous system. Experimental studies evidenced the possible release of acetylcholine by erythrosin in isolated nerve fibers [119]. Other experiments support the concept of "excitotoxins", i.e. substances which can damage immature neurons in the hypothalamus of newborn mice at high doses. Olney used this concept with glutamate [120]. However, the pathogenic action of glutamate in man is debatable, and in fact has been suggested only by Olney [121].

In the central nervous system, only hypotheses based on the knowledge of activator or inhibitor systems, involving glutaminergic, GABAergic, and aspartergic neurons have been proposed. At doses greater than 50 mg/kg (i.e. the ADI set by the FDA), aspartame could stimulate activator neurons via the release of aspartic acid thus presumably explaining psychological disorders: difficulty in intellectual concentration, agitation and sensation of dizziness. However, as 40 mg aspartame have a sweetening potency comparable to 10 g saccharose, it is not realistic to assume that a dose higher than the ADI which correspond to over 30 g aspartame for an adult of average weight could be ingested. Indeed, a recent study evaluated the actual daily intake between 2 to 10 mg/kg/day

[122]. Similarly, gamma hydroxybutyrate caused neurosensory and psychiatric symptoms in which an interference with GABAergic neurotransmission was postulated to be involved [123].

Sodium glutamate was suggested to interfere with glutamatergic neurons, such as GABAergic inhibitor neurons, because glutamic acid is the precursor of GABA. Paresthesias in the upper half of the body which are the major features of the "Chinese restaurant syndrome" described by Kwok, could be attributed to this mechanism [124]. Since glutamic acid and sodium glutamate are also precursors in the synthesis of acetylcholine, high doses of glutamate (>8 g) could facilitate excessive acetylcholine synthesis, a hypothesis proposed by Ghadimi et al. [125] following their observation that healthy volunteers given high doses of sodium glutamate had a decrease in plasma cholinesterases. This effect could explain the bronchospasm of sudden onset, or on the contrary, of late-onset but prolonged, observed in several asthmatic patients [126,127], as well as headaches related to changes in cerebral vasomotricity. Other effects, such as epigastric pain, have been attributed to a gastroesophageal reflux related to a concentrated, hot solution containing sodium glutamate (Chinese soup). Lastly, part of the disturbances might be erroneously attributed to glutamate and caused by biogenic amines (histamine and tyramine), often present at high concentrations in the same foods [128].

The effects of several additives on the sympathetic or parasympathetic limb of the peripheral nervous system have been clearly documented. Caffeine (an additive found in Coca-Cola) has well-known stimulant properties on the sympathetic nervous system. Its effects are accentuated in subjects with excessive adrenergic activity for which sympathetic nerve hyperactivity can be evidenced by different tests such as the isoprenaline test. Metabisulfites release sulfurous anhydride (SO_2) in acidic medium. After ingestion, this process occurs due to the acidic pH of the stomach. Sulfurous anhydride reaches the esophagus and is inhaled triggering a vagal reflex, immediately causing bronchoconstriction in some asthmatic patients. Bisulfite intolerance develops in patients with abnormal bronchial reactivity to parasympathetic stimulation, as evidenced by metacholine or carbamylcholine tests. Interestingly, bronchoconstriction can be induced in normal subjects with higher SO_2 concentrations and prevented in normal subjects as well as in asthmatic patients by prior administration of atropine, thus confirming the involvement of a cholinergic mechanism [22,129]. However, when a muscarinic agonist is used for muscarinic M_2 receptors, prior to the inhalation of SO_2, a clear difference is observed between normal subjects and asthmatic patients. The bronchoconstriction to SO_2 is blocked in normal subjects, but not in asthmatics. As the stimulation of M_2 receptors (located at the endings of post ganglionic fibers) normally inhibits the release of acetylcholine, this finding has led to the postulation of a defect of these receptors in asthmatic patients [130].

In the case of caffeine and metabisulfites, pharmacological effects on the sympathetic and parasympathetic nervous system occur in patients at lower doses than in normal subjects. Using the isoprenaline and metacholine tests, a

variable degree of abnormal reactivity of the autonomic nervous system can be demonstrated. It is legitimate then to postulate the existence of abnormalities of adrenergic or cholinergic receptors. Metabisulfites both in foods and injectable drug formulations pose a high risk. Bronchoconstriction is commonly observed in oral challenge tests with 15 or 30 mg metabisulfites [8,23,112,131]. Based on this finding, the risk is obvious when drinking a glass of wine which usually contains this amount of metabisulfites. The same is true following the intravenous injection of antibiotic or corticosteroid formulations containing about 3 mg, or even with the intragingival injection of a local anesthetic with epinephrine containing metabisulfites [23]. As soon as metabisulfite intolerance was identified, this substance was removed from every anti-asthma aerosol spray medication [76].

Enzyme inhibition probably plays a role in adverse reactions to additives. That the multiplicity of additives ingested simultaneously could potentiate this effect is a matter of concern. A quasi-experimental model in man was the use of mono-amine-oxidase inhibitors (MAOI) as antidepressants. Low doses of tyramine in food (6 mg) caused serious clinical reactions because tyramine is no longer catabolized by MAO due to MAOI treatment whereas doses of 40–60 mg are well-tolerated in non-treated subjects [36]. By analogy, a similar risk due to the inhibition of diamine-oxidase (DAO) (of which 90% is found in enterocytes of the small intestine) by anti-oxidants such as sodium nitrite, vanillin, BHT, and BHA, can be postulated. This would result in pseudoallergic reactions manifested mainly as urticaria, vasomotor headache and gastrointestinal disturbances [36,132,133]. These symptoms may also be directly caused by food histamine insufficiently metabolized because of DAO inhibition.

Several azo colouring agents could inhibit phenol-sulfotransferase resulting in increased susceptibility to the effects of phenols [134]. In this instance, the enzyme inhibition produced by an additive results in reactions to substances other than the additive itself (e.g. phenols in wines).

A lack of degradation of additives due to preexisting enzyme deficiency may result in excessive pharmacological or immunological effects. Metabisulfites may induce late-onset reactions following ingestion of high doses. A defect in hepatic and pulmonary sulfite oxidase [22] could explain the persistence of abnormally high serum and tissue metabisulfite levels inducing an inflammatory reaction due to increased production of oxygen free radicals derived from arachidonic acid metabolism in cell membrane.

METHODS FOR THE DIAGNOSIS OF HYPERSENSITIVITY AND INTOLERANCE TO FOOD ADDITIVES

A long time ago, IgE-dependent allergy was documented using passive cutaneous transfer (Prausnitz–Kustner test) [79,95] which was almost totally abandoned (although still in use in 1986) because of the risk for virus transmission [58]. At the present time, diagnosis of this type of allergy is based on

immediate skin tests (prick tests), intradermal tests, human basophil degranulation test (HBDT) or histamine release from leukocytes (LHR). Identification of specific IgE by radio-immuno or immuno-enzymatic assays is currently available for a number of additives, such as alpha-amylase, lysozyme, papain or carob bean. These methods are all useful when the allergen is a protein or a hapten covalently bound to a protein [42] or a high-molecular-weight substance with several antigenic determinants per molecule (carboxymethylcellulose).

By contrast, most chemical substances are monovalent haptens and the binding of two specific IgE molecules on the surface of cutaneous mast cells (as in skin tests) or on the basophils (as in LHR or HBDT) is rather unlikely, so that positive results are seldom observed with these tests [84]. Appropriate investigations on the mechanisms of hypersensitivity to xenobiotics require the coupling of haptens to sepharose by various activation methods, or, in an initial phase, the coupling of haptens to a carrier protein, with subsequent coupling of the compound to sepharose, in order to detect specific IgE. This technique is only available for formaldehyde [87].

The mechanisms of delayed-onset hypersensitivity and photosensitization can be investigated by patch tests read after 48 hours [20,44,53,82,85,92]. The hapten deposited on the skin gradually penetrates the epidermis where it binds to epidermal proteins and forms a complete antigen. Tests such as the inhibition of leukocyte migration and lymphoblastic transformation have only been used in a few instances [90]. Immunohistological examination of a skin test biopsy is sometimes an element of diagnosis [13,50].

Regardless of the mechanism involved in hypersensitivity, skin tests and available laboratory tests are often unable to identify the mechanism actually involved. From a practical standpoint, another methodology certainly needs to be developed. Whenever a food additive is suspected, a dietary category investigation is undertaken based on a record of foods ingested for a week, according to previously published principles [36]. The collection of all labels from foods ingested during a week indicates which additives should be suspected because of frequent ingestion: they vary considerably from one individual to another, depending on food habits and taste preferences. In a second phase, avoidance of all additives is ordered during a 3-week period before oral challenge tests with the additives suggested by the dietary investigation, are performed using a single- or double-blind design [34,35,131]. One test per day is performed when immediate hypersensitivity is suspected or one test every 3 days at least when delayed-onset hypersensitivity is suspected. The tested dose may be based on the ADI or adjusted to the patient's actual daily ingestion as evaluated by the dietary investigation. When the clinical reaction is eczema or urticaria, challenge tests can be run at home. Tests to be performed in the hospital are selected. If asthma or anaphylactic shock are suspected, challenge tests should be performed under strict medical monitoring. Heart rate, blood pressure, colour of the patient's skin and mucosae, chest auscultation and measurement of peak expiratory flow are the main parameters for monitoring. They are also objective diagnosis criteria. Monitoring must be maintained for 24 hours

because of possible late-onset respiratory allergy. When the reaction is asthma of possible occupational origin, inhalation challenge tests may legitimately be used: either the suspected additive is inhaled as a solution or it is handled and inhaled as a powder [38,66]. A diet based on avoidance of the additives evidenced by these tests provides definitive diagnosis if disappearance of symptoms is noted [13,50,131].

When an anaphylactic-type shock occurs following ingestion of food, the food ingested and the original food packaging must be kept for further investigative purposes. It is thus possible to know which additives were actually involved from the information on the food label or directly from the food manufacturer, or to perform analysis for identifying and assaying the suspected additive [72]. When a severe adverse reaction occurs following the administration of a drug, rechallenge with this drug in a formulation without the additive enables the investigator to observe whether the drug is well-tolerated by the patient, as has been shown for heparin (without chlorocresol), oral cyclosporin (without Cremophor El®) or vitamin B_{12} (without benzyl alcohol). It is not ethical to administer test injections with the suspected additive [19].

CONCLUSION

A series of issues has been raised which in turn have led to a series of questions. Little is known of the mechanisms involved in adverse reactions to xenobiotics in food. This is probably a complex situation: the distinction between pharmacological mechanisms and effects on the immune system may indeed be artificial. Thus, the effects of xenobiotics on neurotransmission could alter the neuromodulation of the immune system. Similarly, enzyme inhibition may have an indirect impact on immune functions. The body is also an environment. Considering the outer environment (macroenvironment) and neglecting the inner environment (the endogenous microenvironment represented by food and the intestinal bacterial flora) would result in a dichotomy of the reality that identical xenobiotics are found in food or drugs or related to atmospheric pollution.

The phenomenon of latent sensitization in relation to the ingestion of trace amounts of a foreign food substance should be emphasized. Even though no clinical signs may be observed, anaphylactic shock may occur when this chemical is injected as a component of a drug formulation (as with patent blue and perhaps carboxymethylcellulose). Conversely, the consequences of ingesting a food additive by a subject sensitized to the additive present in a drug formulation are unknown.

The incorporation of new additives in food by the industry is a serious source of concern. The trend of "health-food products" from the USA carries specific risks exemplified by the eosinophilia-myalgia syndrome or by anaphylaxis to psyllium seeds from cereal products [135]. Honey enriched with propolis or pollens is under study by apiculturists, while the risk of sensitization to

propolis [136,137] is well-known and anaphylaxis following pollen ingestion has been reported. The introduction of dietary proteins, whether natural or modified, as additives, the increasing use of enzymes as manufacturing aids, is another source of more frequent allergic disorders, both for consumers and for workers in the food industry [37].

With regard to new types of food products, is it legitimate to leave innovation solely in the hands of the food industry without considering the risk for dissemination of possible new allergens? Emphasis must certainly be given to the need for evaluating the risk from a substance by assessing its allergenic potential [40,42,63]. An overall reflection on methods for studying allergenic potential, applicable to certain animal species, is becoming an urgent objective for scientists and lawmakers alike.

Generally speaking, we are facing problems posed by (i) the multiplicity of xenobiotics, (ii) the lack of identification for many chemical entities, (iii) the diversity of mechanisms of action which more often are speculative rather than indisputably established, (iv) the impossibility of linking mechanisms to pathological conditions, (v) the lack of knowledge on effects on the immune system of cumulative exposure to dozens or hundreds of chemical substances that are foreign to natural food substances.

For these reasons and for a long time to come, clinicians must focus their attention on the analysis of sporadic cases of clinical adverse events associated with food additives. The dissemination of such cases is the required basis for an allergy monitoring system, required by the increasing incidence of allergic disorders.

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6. Hypnotics, sedatives and antipsychotics

INTRODUCTION

Sedative–hypnotic drugs have in common the ability to induce various degrees of behavioural depression. Hypnotics are used to produce sleep and sedatives are used to relieve anxiety, restlessness and irritation [1]. Barbiturates, benzodiazepines and other minor tranquillizers relieve instability and tension. Often there is no sharp distinction between the two effects, and the same drug may have both actions depending on the method of use.

By contrast, the neuroleptic–antipsychotic agents are used primarily to treat psychotic disorders and have a marked effect on thought disturbances associated with paranoid ideation, delusions, anxiety, and agitation [1]. The main classes of neuroleptic agents are phenothiazines, butyrophenones and thioxanthenes.

These two groups account for the majority of drug-induced poisonings at the present time, both in adults (suicide attempts) and in children (domestic accidents) [2]. They are also one of the most frequent causes for attendance at Poison Control Centres [3] and Emergency Departments [4,5] as well as admission to Intensive Care Units because of acute poisoning [6,7].

BENZODIAZEPINES

In most countries, benzodiazepines are now by far the commonest drug taken in overdosage [8–10] in relation to their increased prescribing as sedative/hypnotics, muscle relaxant, anti-anxiety and anticonvulsant agents, not only because of their efficacy, but also of their remarkable safety [11].

The benzodiazepines, unlike other sedative–hypnotics, have a low order of toxicity, unless ingested with other central nervous system (CNS) depressants. Unfortunately, association with ethanol, cyclic antidepressants, phenothiazines, or drugs of abuse is very common, and the acute somatic risk is substantial [9]. Benzodiazepines are typically divided into three groups according to their respective elimination half-life (Table 6.1) [11,12]. It must be borne in mind that many metabolites are as active, or even more active than the mother drug, and hence, the actual biological half-life may be much longer, accounting for

Ultrashort (<10 hours)		
	Midazolam	2–5 hours
	Prazepam	1–2 hours
	Triazolam	2–5 hours
Short (10–24 hours)		
	Alprazolam	9–15 hours
	Bromazepam	20 hours
	Estazolam	8–31 hours
	Flunitrazepam	9–30 hours
	Loprazolam	5–22 hours
	Lorazepam	8–25 hours
	Lormetazepam	9–15 hours
	Nitrazepam	18–48 hours
	Oxazepam	3–21 hours
	Temazepam	7–17 hours
Long (24 hours)		
	Chlorazepate	36–200 hours
	Chlordiazepoxide	5–30 hours
	Clobazam	10–49 hours
	Clonazepam	10–50 hours
	Desmethyldiazepam	51–120 hours
	Diazepam	14–70 hours
	Flurazepam	40–200 hours
	Medazepam	70 hours
	Quazepam	25–41 hours

Table 6.1. *Classification of benzodiazepines according to elimination half-life*

discrepancies between the evolution of plasma concentrations of the ingested drug (e.g. diazepam) and the observed clinical effects which are also due to active metabolites (e.g. desmethyldiazepam, temazepam and oxazepam in the case of diazepam).

Toxic and lethal dosage

As a guide, Table 6.2 lists the toxic doses of major benzodiazepines as suggested by recent reviews [13,14]. Overall, short-acting benzodiazepines are considered to be more toxic when equal doses have been ingested.

No fatalities solely due to the oral ingestion of a benzodiazepine derivative have been documented although several poorly documented papers reported deaths related to diazepam, triazolam and other derivatives, especially in elderly patients with severe underlying illness [15–17].

Toxicokinetics

The majority of benzodiazepines are rapidly and almost completely absorbed (bioavailability 80–100%) after an oral dose. Peak plasma concentrations are

Benzodiazepine	Adults	Children
Alprazolam	15 mg	0.1 mg/kg
Bromazepam	500 mg	5 mg/kg
Chlorazepate	500 mg	5 mg/kg
Chlordiazepoxide	500 mg	8 mg/kg
Clobazam	100 mg	1 mg/kg
Clotiazepam	>30 mg	1 mg/kg
Diazepam	500 mg	5 mg/kg
Estazolam	20 mg	0.02 mg/kg
Flunitrazepam	20 mg	0.1 mg/kg
Loflazepate	60 mg	0.2 mg/kg
Lorazepam	100 mg	1 mg/kg
Medazepam	500 mg	5 mg/kg
Nitrazepam	50 mg	5 mg/kg
Oxazepam	400 mg	5 mg/kg
Prazepam	100 mg	1 mg/kg
Tofisopam	3000 mg	30 mg/kg
Triazolam	5 mg	0.05 mg/kg

Table 6.2. *Range of benzodiazepine toxicity*

usually reached between 1–3 hours post-ingestion. Benzodiazepines are highly bound to plasma proteins (70–99%). Alcohol can delay and antacids can reduce the absorption of several benzodiazepines [11].

All benzodiazepines are highly lipid-soluble and readily distributed among body tissues. As expected, the volume of distribution (Vd) is high for the majority of these drugs (Table 6.3) [11,12,17,18].

Benzodiazepines are eliminated almost exclusively by hepatic metabolization. Biotransformation follows two major pathways. The first consists of oxidative reactions such as hydroxylation or demethylation, which produces one or more active metabolites that can partially or totally account for the pharmacological effects of the drug. The second pathway is hepatic conjugation leading to inactive metabolites [11]. Cimetidine increases the elimination half-life and reduces the plasma clearance of several benzodiazepines (e.g. diazepam) by inhibiting hepatic microsomal enzymes. The elderly have both reduced metabolism and increased sensitivity to a given dose of benzodiazepines [12].

Pathophysiology

Benzodiazepines facilitate neurotransmission in the gamma-aminobutyric acid (GABA) synapses, by interacting with two types of GABA receptors and blocking the ability of cells to conduct nerve impulses [11]. A good correlation has been found between the affinity of benzodiazepines for specific receptor sites and their potency as anxiolytics, anticonvulsants, muscle relaxants and sedative–hypnotics. By binding to the polysynaptic terminals where GABA is

Benzodiazepine	Vd (l/kg)
Alprazolam	0.97–1.17
Chlordiazepoxide	0.26–0.58
Clobazam	0.9–1.8
Clonazepam	3.2
Chlorazepate	0.16–0.5
Desmethyldiazepam	0.9–1.3
Diazepam	0.95–2
Flurazepam	3.4
Loprazolam	4
Lorazepam	0.8–1.6
Midazolam	0.8–1.5
Nitrazepam	1.5–2.8
Oxazepam	0.5–2
Prazepam	9.3–19.5
Quazepam	5–8.6
Temazepam	0.75–1.4
Triazolam	0.7–1.5

Table 6.3. *Apparent volume of distribution of the benzodiazepines*

released, benzodiazepines cause hyperpolarization and potentiate GABA [12]. They can also potentiate the effect of other CNS depressants (e.g. psychoactive drugs or ethanol).

Clinical presentation

The central nervous system is the target organ of benzodiazepine overdose. The severity of CNS depression is influenced by the dose, the patient's age and his clinical status prior to ingestion as well as co-ingestion of other CNS depressants, as recently reviewed [11].

The initial, and in the majority of cases, the only clinical manifestations are sedation, sleepiness, lethargy, slurred speech, ataxia and nystagmus. With pure and mild to moderate benzodiazepine ingestions, patients may develop agitation and disorientation, and experience memory loss and confusion. Dilated pupils may be present but myosis is more frequently noted.

At high doses, patients may be comatose, but if the coma is profound, the ingestion of ethanol or other hypno-sedatives should be suspected. The duration of coma following benzodiazepine overdose ranges from 12 to 36 hours in most cases, but is influenced by several factors. Elderly and very young children are clearly more susceptible to the CNS depressant action of benzodiazepines.

In the usual dose range found in poisoned patients, benzodiazepines have no direct toxic effects on the cardiovascular as well as respiratory systems. Respiratory depression with alveolar hypoventilation and hypotension occurs only with very large doses of benzodiazepines, rapid intravenous injection or the

ingestion of other CNS depressants [9]. There are no reports of either renal, hepatic or gastrointestinal toxicity, or other target organs following benzodiazepine overdose although one report referred to adult respiratory distress syndrome associated with flurazepam overdose [19].

Benzodiazepine overdoses in pregnant women have seldom induced serious morbidity in either the mother or the fetus, although large doses of benzodiazepines administered near delivery may induce respiratory depression in neonates. The teratogenic potential of benzodiazepines remains controversial, but is probably small if it exists at all [11].

Dependence and withdrawal syndrome

There is clear evidence that prolonged use of even therapeutic doses of benzodiazepines lead to dependence [11]. The abrupt withdrawal from benzodiazepines, especially in those people using short-acting benzodiazepines (e.g. lorazepam), may begin a few days after cessation of the drug. The severity of withdrawal varies with dosage and duration of use. The most common symptoms are hallucinations, confusion and seizures [20].

Laboratory analysis

In benzodiazepine poisonings, the role of the laboratory is usually restricted to confirming or rejecting clinical suspicions by qualitative analysis. Due to the phenomenon of tolerance, frequent co-ingestion of other drugs, active metabolites and the large volume of distribution of many benzodiazepines, little if any correlation between plasma concentrations, clinical symptoms and prognosis can be clearly identified. Therefore toxicological analysis is usually based on other grounds such as coma of unknown origin, mixed or deep coma [21].

The therapeutic plasma concentrations range between 0.3 and 0.6 mg/l for diazepam and are less than 0.75 mg/l for temazepam. Lethal temazepam poisonings with plasma concentrations between 0.9 and 14 mg/l have been reported [22,23]. No specific laboratory analysis is needed unless otherwise indicated.

Diagnosis

Patients with pure benzodiazepine overdose display mild to moderate sedation, often with dysarthria and ataxia, but no serious neurologic, cardiovascular, or respiratory impairment. There are no pathognomonic clinical features or specific toxicologic syndromes, and the diagnosis is based on the patient's history and the physical examination, and is confirmed by laboratory analysis [18].

The presence of deep coma, hyperreflexia or clonus, cardiovascular instability, and respiratory depression requiring assisted ventilation, suggests an alternative diagnosis or the concomitant ingestion of ethanol, tricyclic antidepressants, phenothiazines, etc. [18]. Flumazenil can facilitate the differential diagnosis in patients with coma of unknown origin [24].

Treatment

The current therapy of benzodiazepine overdose is generally conservative and supportive ("Scandinavian method"). In patients with respiratory or cardiovascular failure, airway protection and mechanical ventilation should be instituted if patients are unresponsive to the benzodiazepine antagonist, flumazenil. Circulatory support should consist of placing the patient in the Trendelenburg position and administering intravenous crystalloid fluids; in those rare cases unresponsive to these measures, vasopressive drugs (e.g. dopamine) should be administered [18].

Large ingestions or symptomatic patients require emesis or gastric lavage if this can be performed within 2–3 hours of the ingestion, followed by activated charcoal, but standard precautions based on the patient's level of consciousness and the adequacy of airway protection should always be contemplated [18]; however in pure benzodiazepine overdoses, gastric emptying has not been shown to decrease mortality conclusively and is therefore not routinely required. On the other hand, the administration of activated charcoal in mild to moderate benzodiazepine poisonings has seemingly no influence on the clinical outcome, but it is presumably preferable to administer charcoal to all patients with a deliberately ingested overdose as it is difficult to predict which patients will develop severe benzodiazepine-related toxicity.

There are no practical ways to enhance benzodiazepine elimination significantly. Forced diuresis is of no proven value. Hemodialysis and peritoneal dialysis are relatively ineffective to remove clinically significant amounts of benzodiazepines because of extensive protein binding [18]. Hemoperfusion has not been well evaluated [12].

Although several drugs have been noted to reverse some effects of benzodiazepines in poisoned patients, the antidote of choice is the 1,4-imidazobenzodiazepine, flumazenil. This is a competitive antagonist which reverses rapidly and completely all central effects of benzodiazepines, and an effective and safe antidote in benzodiazepine overdoses [25–28].

Various guidelines have recently been proposed for flumazenil use. The most frequently recommended initial dose is an iv bolus of 0.25 mg, repeated each minute if the patient does not recover consciousness, up to a maximum of 2 mg. The majority of patients respond after 1–5 minutes with 0.25–0.75 mg flumazenil in pure benzodiazepine ingestion or when combined with ethanol, or with 0.50–1.50 mg if there is co-ingestion of other psychoactive drugs [29]. Patients who do not respond to a dose of 2 mg flumazenil are unlikely to respond with higher doses, but some patients with mixed poisonings have responded to 10 mg flumazenil [24]. Flumazenil can also be used prior to hospital admittance [30].

The antagonist effects are short lived, due to a half-life of approximately 1 hour; 15 to 60 minutes later, repeated doses of 0.25 mg or a continuous infusion (0.25 mg/hour) may be required (especially in poisonings with long-acting benzodiazepines or in the elderly) to maintain the desired level of consciousness

[27,29,31–33]. Flumazenil has also been used in children at repeated doses of 10 μg/kg [34] and recently in a neonate with recurrent apnea due to prenatal benzodiazepine exposure (0.02 mg/kg intravenous loading dose followed by 0.05 mg/kg/hour) [35].

The most common side-effect of flumazenil is agitation [29,31,36]; in this case, it is better to stop the bolus or to slow the infusion rate. Flumazenil has been noted to precipitate convulsions in epileptic patients on benzodiazepines for seizure control and in patients with co-ingestion of drugs lowering the seizure threshold (e.g. tricyclic antidepressants). In such cases, the use of flumazenil must be strictly monitored; if a seizure develops, it must be controlled by stopping the antidote and injecting intravenous benzodiazepines immediately. As with naloxone in the treatment of opiate intoxication, flumazenil has the potential to precipitate withdrawal symptoms in benzodiazepine-dependent individuals [37].

Although the potential toxicity of benzodiazepines is relatively low, and an aggressive therapy is seldom required in pure benzodiazepine poisonings, it has been suggested that flumazenil offers several important potential uses in clinical medicine. As flumazenil reverses benzodiazepine-induced central nervous system depression only, it has a diagnostic as well as therapeutic value. Obviously, by assuming that all provided information has been taken into consideration, a suspected diagnosis of benzodiazepine overdose can be confirmed or conversely benzodiazepine poisoning can be excluded as a cause of CNS depression in an undiagnosed patient [25,27,38]. In comas secondary to multiple drug ingestions, removing the benzodiazepine component may avoid the need for intubation and mechanical ventilation [8,25,27,32,39]. In pure benzodiazepine overdose, flumazenil can speed up recovery, reduce after-effects and shorten hospital stay.

Patients without evolutive complications, who are asymptomatic and able to walk without ataxia after treatment and after 4 to 6 hours of observation, can be discharged after appropriate psychiatric consultation in cases of voluntary ingestion.

In withdrawal syndromes, initial symptoms should be treated with diazepam or phenobarbital; the dose may then be reduced gradually at a rate of about 10% per day of the initial dose required to control symptoms. Propranolol 20 mg three to four times daily, starting on the 5th day and continued for two weeks, has been shown to be useful in benzodiazepine withdrawal [40,41]. Status epilepticus usually requires admission to the Intensive Care Unit and the use of high doses of short-acting barbiturates.

OTHER SEDATIVE–HYPNOTICS

At the present time, poisonings due to these drugs are less frequent than those due to benzodiazepines. However, various clinical manifestations are relatively specific and warrant adequate therapeutic measures.

Meprobamate

Meprobamate, introduced in clinical practice in 1955 as a minor tranquillizer, exerts sedative as well as myorelaxant properties.

In adults, compared with the therapeutic dose of 600–1600 mg/day, 4–10 g is a toxic dose and 12–40 g is a potentially lethal dose. Therapeutic plasma concentrations are approximately 10 mg/l; at plasma levels greater than 40 mg/l, side-effects may develop, between 60 and 120 mg/l impaired consciousness and superficial coma, and between 100 and 240 mg/l deep coma. However, daily users may develop tolerance [42].

Meprobamate is only slightly hydrosoluble and absorbed mainly in the small intestine. At therapeutic doses, maximum plasma concentrations are reached 2–3 hours after ingestion. Gastric conglomerates are readily produced and may account for slow and continued absorption. The volume of distribution is 0.75 l/kg, and the binding to plasma proteins is 15%. At least 90% of meprobamate is metabolized in the liver with a half-life of 8–12 hours at therapeutic doses and up to 27 hours following acute ingestion.

Acute poisoning is characterized by depression of the CNS (ataxia, disarthria, nystagmus, lethargy, stupor, coma), myosis or mydriasis, convulsions, hypothermia, respiratory depression, hypotension due to reduced systemic vascular resistances which may be independent of the severity of coma, and myocardial depression which may lead to cardiogenic pulmonary edema [43]. Arrhythmias, tachycardia and bullous cutaneous lesions have also been reported.

Laboratory analysis will confirm the diagnosis and can indicate the severity of poisoning (severe if plasma level is >100 mg/l). However, due to the tolerance, the ingestion of other psychoactive drugs and age, laboratory analysis and clinical symptoms may not correlate [42].

As regards treatment, besides the usual measures of respiratory and hemodynamic support, care must be taken in the use of plasma expanders and fluid charges in the treatment of hypotension, due to the risk of cardiogenic pulmonary edema. Hemodynamic monitoring by Swan–Ganz catheter and the use of vasopressive drugs have been recommended in severe hypotension [43].

Gastric emptying and repeated activated charcoal (0.1–0.5 g/kg/6 hours) are early therapeutic measures [43–46]. Aspirative gastroscopy is recommended if gastric conglomerates are suspected [43]. Forced diuresis is not effective and may be associated with a high risk for acute pulmonary oedema [43,45].

In severe poisonings confirmed by clinical and analytical criteria, hemoperfusion in charcoal or resin cartridges should have top priority in treatment because higher levels of meprobamate are extracted with this method than with hemodialysis [42,45,47–50].

Methaqualone

Methaqualone is a hypno-sedative drug with clinical effects similar to those of barbiturates. Due to its capacity to produce euphoria at small dose levels and

its popular reputation as an aphrodisiac, acute poisonings became relatively frequent in the 1980s [51].

Hypnotic effects are obtained by oral doses of 150–400 mg in adults. In children, one tablet (150 mg) is considered toxic, whereas in adults a dose greater than 800 mg may be toxic. Plasma levels above 25 mg/l should be considered as indicative of severe poisoning [52], but tolerance that may develop with chronic use (75–2000 mg/d) [53]. The time elapsed since ingestion and the concomitant intake of other hypno-sedatives or ethanol, must be taken into account when interpreting plasma levels, as is true with most psychoactive drugs.

Methaqualone is rapidly absorbed by the digestive tract, reaching peak plasma concentrations 2–3 hours after ingestion of a therapeutic dose. 75% is protein-bound. Methaqualone is highly lypophilic with a Vd of 6 l/kg [54]. Metabolization is predominantly hepatic with only 5% excreted unchanged through the kidneys. The biphasic half-life between 20 and 50 hours is prolonged in intoxicated patients.

Acute poisoning may lead to CNS depression (somnolence, ataxia, paresthesias, agitation, convulsions and coma), frequently associated with hypertonicity, increased tendinous reflexes and myoclonias [53]. Hypotension and apnea occur less frequently than in poisonings with unrelated hypno-sedatives. Pulmonary oedema may occur, and forced diuresis should therefore be avoided. Cystitis, conjunctive hemorrhages, thrombocytopenia and petechias have all been reported. A withdrawal syndrome may occasionally occur during the patient's stay in the hospital, manifesting as severe generalized convulsions [52].

As regards treatment, the use of myorelaxants and even curarizing agents may be indicated in addition to usual measures, such as respiratory and hemodynamic support [52]. Gastric emptying and repeated oral activated charcoal should be used very early. In severe clinical situations with plasma levels above 40 mg/l, prolonged hemoperfusion has been recommended [47,48, 55]. Hemodialysis and forced diuresis have no therapeutic value in this situation.

Glutethimide

As it easily induces addiction and withdrawal syndrome, glutethimide is one of the less frequently prescribed hypno-sedatives. The ingestion of glutethimide and codeine ("loads") constitutes a form of drug addiction [56,57].

The normal hypnotic dose in adults lies between 250–500 mg orally. The ingestion of 3 g is considered as toxic, and of 10 g (150 mg/kg) as potentially lethal. Glutethimide plasma levels correlate neither with the depth of coma [58] nor with the concentration of the metabolite hydroxyglutethimide [56]. As a guide, plasma levels above than 30 mg/l may be considered lethal [59].

Gluthetimide is only slightly hydrosoluble, which delays absorption in the gastrointestinal tract. Peak plasma levels of 2.9–7.1 mg/l are reached between 1 and 6 hours after the ingestion of 500 mg [56]. Enterohepatic circulation exists. 50% is protein-bound in plasma. Due to its high lypophilicity, the Vd is 2.7 l/kg [60]. Plasma concentrations decline biphasically after a therapeutic

dose: the first phase is short with a 4-hour half-life and the second phase is slower with a 11-hour half-life. In acute poisonings, the half-life may be prolonged up to 40 hours. The drug is metabolized in the liver with active metabolites which account for changes in the level of consciousness in acute poisonings [60]. Clinical manifestations include coma of fluctuating intensity, anticholinergic syndrome (mydriasis) and the possible association with hypotension cerebral oedema, convulsions, apnoea, cardiovascular depression, hypothermia, bullous cutaneous lesions and pulmonary oedema [60,61].

Many glutethimide poisonings are treated successfully by supportive methods [58,62] and gastrointestinal decontamination. Enteric depuration with repeated doses of activated charcoal also interrupts enterohepatic circulation and is effective [44,46,56]. Hemoperfusion is limited to severe cases which do not respond to the above mentioned measures, usually when plasma levels are above 40 mg/l [59]; the best extraction is obtained with anionic resin cartridges (Amberlite). Deterioration posterior to extractive techniques may occur due to a plasma rebound phenomenon caused by either redistribution of the drug or enterohepatic circulation [55,60].

Ethchlorvinol

Ethchlorvinol is supplied as gelatine capsules containing 0.5 ml of a liquid composed of ethchlorvynol and polyethylene glycol. Acute poisonings following both oral ingestion and intravenous injection of the capsule content have been reported [63,64]. Oral overdose (the normal therapeutic dose is 500–750 mg in adults) is produced by ingestion of 4–10 g, and may be lethal between 10–25 g or as little as 2.5 g if associated with ethanol. Therapeutic plasma levels are considered to be 5 mg/l, light poisoning 20 mg/l and potentially lethal poisoning over 150 mg/l [55,59,60].

At therapeutic doses the drug is absorbed rapidly by the gastrointestinal tract, and is distributed in fatty tissues due to its lypophilicity. It is 50% protein-bound and the Vd is 2.8 l/kg [54,60].

Clinical symptoms of oral poisonings are those commonly seen with other hypno-sedatives; in some cases, prolonged coma and increased salivation mimicking cholinergic poisoning (e.g. organophosphates insecticides) have been described. Following parenteral administration it readily produces immediate noncardiogenic pulmonary oedema which has been shown to be unrelated to polyethylene glycol [61,63–65]. Ethchlorvynol may have a direct effect on pulmonary endothelial cells [66].

Depending on the severity of the pulmonary oedema, if present, tracheal intubation, mechanical pulmonary ventilation and positive-end expiratory pressure (PEEP) are primordial supportive measures. Gastric emptying and oral activated charcoal can be useful early [46]. If clinical criteria of severe poisoning are present and plasma levels above 150 mg/l, prolonged extraction by hemoperfusion with Amberlite or activated charcoal cartridges is indicated [59,67,68]. Although high extraction levels can be achieved, the

extracorporeal technique must be prolonged because of high corporeal drug deposits [48,55,60].

Chloral hydrate

Chloral hydrate acts as a hypno-sedative only after metabolisation by alcohol-dehydrogenase to trichloroacetic acid and trichloroethanol; the latter is an active metabolite responsible for the hypno-sedative, pharmacological and toxic effects of the drug.

The therapeutic dose is 250 mg in adults and 8 mg/kg in children. A lethal dose is between 4 and 30 g. At therapeutic doses the half-life is 4–12 hours, but up to 35 hours in overdoses [55,60]. Chloral hydrate and trichloroethanol are 40% and 80% bound to plasma proteins, respectively. The Vd is 0.6 l/kg [54].

Overdose produces irritation of the gastro-oesophageal mucosa and clinical symptoms which mimic ethanol poisoning with a risk of cardiorespiratory depression and often ventricular arrhythmias [69,70]. Albuminuria and jaundice have been reported.

As regards treatment, gastrointestinal extraction techniques (emetics, gastric lavage, cathartics and activated charcoal) together with general supportive measures and treatment of complications are indicated. Hemodialysis and hemoperfusion are effective and indicated in severe intoxications when plasma levels are above 50 mg/l [55,59,60].

ANTIPSYCHOTICS

Antipsychotics or neuroleptics are a group of drugs which alter the individual's behaviour, among other things, by creating a state of psychomotor indifference and diminishing excitation, aggression and agitation. They are widely used in the treatment of a large number of psychiatric illnesses (psychosis, schizophrenia, hallucinatory and delirious states) [71,72].

Following their introduction in the early 1950s, fewer psychiatric patients have been hospitalized, because they can be managed by out-patient clinics. At the same time the number of acute poisonings, both accidental and voluntary, has increased. Table 6.4 lists the most frequently used neuroleptics [71].

Toxic and lethal dose

The toxic dose levels of antipsychotics are not well established due to the wide therapeutic index and the frequent simultaneous ingestion of other psychopharmaceutics. Table 6.5 gives the approximate toxic doses of the main antipsychotics [13]. Children appear to be more susceptible than adults. Deaths due to antipsychotics overdoses are very infrequent, but have been described, for example, after the ingestion of phenothiazines: 20–74 mg/kg in children and 2000 mg in adults.

Phenothiazine derivatives
Aliphatics: chlorpromazine, levomepromazine
Piperidines: thioridazine, piperacetazine
Piperazines: thioproperazine, trifluoperazine, butaperazine, prochlorperazine
Butyrophenone derivatives: haloperidol
Thioxanthene derivatives: flupentixol, chlorprothixene, thiothixene
Benzamides: sulpiride, tiapride
Dibenzoxazepine derivatives: loxapine
Dibenzotiazepine derivatives: clozapine

***Table 6.4**. Classification of the main neuroleptic–antipsychotic drugs*

Neuroleptics	Adult (mg)	Children (mg/kg)
Acepromazine	500	5
Alimemazine	100	3
Benperidol	20	0.5
Chlorpiperazine	200	4
Chlorproethazine	500	10
Chlorpromazine	1500	20
Fluanisone	500	5
Fluphenazine	4000	20
Haloanisone	500	5
Haloperidol	50	1
Isothipendyl	400	50
Levomepromazine	1000	20
Methylperidol	50	1
Moperone	50	1
Pericyazine	200	1
Perphenazine	200	4
Pipamperone	1200	20
Prochlorperazine	500	10
Profenamine	1000	20
Promethazine	1000	20
Sulpiride	1000	
Thioproperazine	100	1
Thioridazine	1000	20
Tiapride	4000	50
Trifluoperazine	100	3
Trifluopromazine	5000	2
Trifluperidol	20	0.5

***Table 6.5**. Range of the main neuroleptics toxicity*

Pharmacokinetics

The oral absorption of chlorpromazine, the prototype compound, is erratic, limited (10–69% bioavailability) and slow. Peak plasma concentrations are reached 2–3 hours after ingestion. The drug is 95–99% protein-bound, and because of its lipophilicity has a large volume of distribution (20 l/kg). The elimination half-life for the parent compounds is, in general, very long (average = 15–30 hours). The elimination is fundamentally by hepatic metabolization (glucuronoconjugation and also sulphoxidation).

Pathophysiology

The activity of neuroleptics is typically defined by their efficacy in treating symptoms of psychoses, such as delirious ideas and hallucinations, and the production of extrapyramidal manifestations by blocking cerebral dopaminergic receptors. In addition, all neuroleptic-antipsychotics have similar pharmacodynamic properties, which consist of blocking histaminic, adrenergic, muscarinic and serotoninergic receptors, although the unwanted side-effects (sedation, hypotension, anticholinergic and extrapyramidal effects) vary widely from one drug to another [72,73].

These drugs are depressants of the CNS by inhibiting the ascendant reticular system, which is responsible for wakefulness. In general the depression is shallow, with deep coma and cardiorespiratory failure only possible following large overdoses, due to the relationship between the ascendent activating reticular system and bulbary centres. Depression of the hypothalamus produces vasodilation which contributes to hypotension and hypothermia, although some patients may develop hyperthermia.

The most characteristic toxic effects occur in the basal ganglia, where dopaminergic receptors are blocked, giving rise to the predominent cholinergic effects, and leading to extrapyramidal manifestations typical of these poisonings [71]. Phenothiazines, also, lower the seizure threshold.

Effects on the cardiovascular system, which are frequent, particularly with piperidine and piperazine derivatives, have a similar origin to those of the tricyclic antidepressants even though they tend to be less severe. Thus, neuroleptics are hypotensive and have a negative inotropic effect, with alterations in cardiac conduction and rhythm.

The muscarinic blockade contributes to sedation, sinus tachycardia and delays in gastric emptying, and the α-adrenergic blockade to hypotension.

Clinical presentation

The patient may present with mild symptoms, for example sensory obnubilation, disorientation, slurred speech and ataxia [71]. Extrapyramidal manifestations are characteristic. At first the patient cannot remain quiet. This is followed by oculogyric crisis with deviations of the vision and buccolingual

crises with facial distortions and other movements, finally giving rise to torsion dystonias in the neck (stiff neck) and trunk (opisthotonos) with forced extension of the extremities. In old people this may present as a syndrome similar to Parkinson's disease with masked face, sialorrea, monotonous speech, hypertonia, trembling and dragging walk.

If the overdose is massive, as is common in suicide attempts, extrapyramidal symptoms are more severe and the patient is deeply comatose, sometimes with convulsions and hemodynamic instability, and changes in the cardiac rhythm and conduction may evolve to ventricular fibrillation. Hyperthermia which is difficult to control has a bad prognosis [71].

Peripheric anticholinergic signs (decreased bowel sounds, urinary retention, skin flushing, dry mucous membranes, mydriasis and tachycardia) are usually noted. Non cardiogenic pulmonary oedema and ischemic enteritis have been also described in severe poisonings [74].

Laboratory analysis

Plasma neuroleptic levels are not clinically useful in overdose. Forrest's colorimetric reaction is usually used to confirm the presence of phenothiazine derivates in the urine, but has the disadvantage of cross-reacting with the tricyclic antidepressants.

Neuroleptic malignant syndrome

The neuroleptic malignant syndrome (NMS) was first described by Delay and Deniker in 1968. It is usually a fulminant and life-threatening idiosyncratic reaction to neuroleptic treatment, which normally occurs between 5 and 15 days after treatment is begun [75,76]. However it has also been described in monoaminoxidase inhibitors intoxication and in patients with Parkinson's disease following withdrawal or reduction of levodopa or other dopaminergic drug therapy [77]. It is characterized by the combination of high-grade fever (>40°C), muscular rigidity, tremors and fasciculations as well as sensory obnubilation [75,76,78,79]. The only consistent biochemical abnormalities are increased creatinine kinase activity, leucocytosis and low serum iron concentration [80,81]. The mortality rate may be as high as 20% and is directly related to delays in diagnosis and the lack of adequate aggressive therapy.

These symptoms are produced by a dopaminergic blockade in the basal ganglia and hypothalamic receptors, with a relative depletion of dopamine in postsynaptic central receptors [75,76,78,79]. This syndrome develops in 0.1–1% of all patients receiving neuroleptics and predisposition to this syndrome may be genetic [82,83].

The hyperthermia, which is a constant feature of NMS, is due to a central change in the regulation of body temperature, although the augmented muscular activity (contraction) which generates heat at the peripheric level by alterations of the nigrostriatal pathway is also involved.

Plasma creatinine phosphokinase is always elevated, and may reach levels greater than 30,000 UI/l which can give rise to oliguric renal failure [75].

NMS should be differentiated from infectious diseases [84], catatonia (but in some cases catatonia can be a harbinger of NMS) [85], malignant hyperthermia and heatstroke [75,78].

Treatment

As with other psychopharmaceutics, initial treatment of acute neuroleptic poisonings must be focused on the CNS and the respiratory and cardiovascular systems, by applying supportive measures as required. Free airways and adequate ventilation should be guaranteed. In cases of hypotension, the patient should be placed in the Trendelenburg position and the volemia expanded by infusion using a 0.9% solution of sodium chloride or Ringer lactate; when there is no response to these measures, a vasopressor with direct α-adrenergic action (e.g. norepinephrine) should be used.

If there are ventricular arrhythmias, acidosis must be ruled out and corrected if necessary (the infusion of sodium lactate or sodium bicarbonate has been proposed), then lidocaine or phenytoin are the antiarrhythmics of choice. "Torsade de pointes" requires treatment with isoproterenol, and severe conduction blockades associated with low cardiac output need sodium bicarbonate or sodium lactate infusion.

Convulsions should be treated with repeated doses of diazepam or clonazepam, and hypothermia by usual rewarming methods.

For digestive decontamination, ipecac syrup or gastric lavage are applicable. These measures are useful during the first 4–6 hours in conscious patients and up to 8–12 hours in comatose patients due to the delay in gastric emptying. Subsequently, activated charcoal is administered (initial dose 1 g/kg) and repeated in severe cases (0.5 g/kg) every 3 hours together with a cathartic [46]. The kinetic features of neuroleptics (above all their wide volume of distribution) account for the ineffectiveness of forced diuresis and extra-corporeal depuration techniques.

No specific antidotes are available. Extrapyramidal dystonic reactions may be treated with biperidene (5 mg iv or im), diphenydramine (1–2 mg/kg up to 50 mg/dose im or iv over 2 minutes) or benztropine mesylate (1–2 mg iv), which usually must be repeated regularly, given the long half-life of the neuroleptics. Severe anticholinergic manifestations (delirium, hallucinations, supraventricular tachyarrhythmias) may respond to physostigmine (1–2 mg iv over 2 minutes) which can however induce severe disturbance of the cardiac conduction.

The neuroleptic malignant syndrome requires adequate cardiorespiratory support (because respiratory complications are very frequent), correction of hydroelectrolytic disturbances (in particular dehydration secondary to hyperthermia and hyperventilation) and alkaline diuresis to prevent acute renal failure due to myoglobinuria. In addition, the use of dantrolene [86], a peripheral muscle relaxant which limits fever and rhabdomyolysis, at a dose of 2.5

mg/kg/6 hours iv, and bromocriptine, a dopaminergic receptor agonist which can reverse tremor, muscle rigidity and obnubilation at a dose of 5 mg/8 hours orally, have been recommended [75,76,78,79,87].

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7. Antidepressants

INTRODUCTION

Tricyclic antidepressants have been widely used since the late fifties and the early sixties. These drugs are prescribed for various disorders such as endogenous melancholy, insomnia, chronic pain, nocturia, anxiety, premenstrual tension and panic disorders. Tricyclic antidepressants have become the agents of choice for treatment of depression and are consequently commonly used in suicidal attempts.

Poisoning with tricyclic antidepressants is a global issue and the American Association of Poison Control Centres reported 39,098 cases with 194 fatalities in the USA in 1992 [1]. Antidepressants was the category of drugs with the highest incidence of deaths in this report. They cause nearly 300 deaths each year in Britain [2]. In Sweden, the antidepressants account for 15–20% of all fatal poisonings. The majority of patients who die, do so before entry to hospital, and hospital mortality is around 1–3% [3–7]. In several recent reports, amitriptyline was the most frequent agent causing death [8,9]. A number of recent antidepressants have been introduced and will be considered at the end of this chapter.

EPIDEMIOLOGY OF ACUTE POISONINGS

Patients admitted to hospital are often young, between 20 and 40 years of age [10]. However, the risk of death increases with age. Patients are predominantly women with a ratio of 2:1 after an overdose, but when fatalities only are considered, the sex ratio women/men is 1:1.3, supposedly reflecting the more determined action of men [11]. Repeated overdose is also more common among men and increases the risk of a fatal outcome [12].

Tricylic antidepressants are commonly available as 10-, 25- or 50-mg tablets. In general, mild poisoning is associated with intake of approximately 500 mg; moderate poisoning develops following the ingestion of 500–1000 mg and severe poisoning when more than 2000 mg are ingested. The individual tolerance towards toxicity is wide and the varying toxicity among antidepressants should also be taken into account.

CLINICAL FEATURES

The clinical features of tricyclic antidepressant poisoning is characterized by symptoms from the peripheral autonomic system, the central nervous system, the respiratory system and the cardiovascular system [13].

Symptoms from the peripheral autonomic system are dry mouth, blurred vision, dilated pupils, retention of urine, constipation, pyrexia and absent bowel sounds. The patient becomes "anticholinergic".

Symptoms from the central nervous system are twitching, convulsions, drowsiness, coma, delirium, pyramidal signs, choreoathetosis, rigidity, hallucinations and ophthalmoplegia.

Symptoms from the respiratory system can be respiratory depression with hypoxemia, aspiration pneumonia, or pulmonary oedema with development of the adult respiratory distress syndrome (ARDS) [14–18].

Symptoms from the cardiovascular system are sinus tachycardia, EKG abnormalities with prolonged PR and QRS intervals, ST- and T-wave changes and various degrees of conduction block, vasodilatation, cardiogenic shock, ventricular fibrillation and finally asystole [13].

Mild poisoning may be characterized by excitation, twitching, dilated pupils, tachycardia, mild hypotension or even hypertension [19]. Severely poisoned patients present with coma, convulsions, profound hypotension, respiratory depression and various arrhythmias.

The clinical course should be carefully monitored as patients with only mild initial symptoms may quickly deteriorate, often following general seizures [20,21]. In the study by Ellison [21] of 30 patients presenting with seizures, mortality was as high as 10%. On the other hand, a patient with a rising level of consciousness and decreasing QRS-interval principally is safe.

The best way to determine the severity of antidepressant poisonings is to measure the QRS-interval on EKG and determine the level of consciousness. Ominous signs are a QRS-interval over 100 msec and deep unconsciousness. Hultén et al. [22] found coma grade to be the best predictor of outcome. Boehnert and Lovejoy [23] found that QRS duration predicts the risk of seizures and ventricular arrhythmias. Clinicians should be alerted for seizures when the QRS interval is over 100 msec and for ventricular arrhythmias when the interval is over 160 msec.

When severe symptoms develop, they normally do so within the first 6 hours [24]. In a study by Callaham and Kassel [4] of 18 fatal cases, with the exception of two, all patients developed major signs of toxicity within 2 hours of arrival at the hospital, and the mean time from arrival to death was only 5.43 hours. Half the fatal cases presented with only mild initial symptoms of poisoning, but deteriorated unfavourably within one hour. All deaths in this report at greater than 24 hours was from complications such as hypoxic brain damage or respiratory failure and pneumonia. The most frequent symptom of these fatal cases before arrival to hospital was unconsciousness. Moreover, only 50% of the patients were hypotensive at the

emergency department and only 11% developed ventricular arrhythmia initially.

TREATMENT

Treatment of poisonings with tricyclic antidepressant drugs is initiated by restoring respiration and circulation. Hypoxemia should always be avoided and mechanical ventilation shall be instituted liberally. When ventilation and circulation is restored, prevention of absorption should be performed.

Gastric lavage

Gastric lavage is recommended when more than 10 mg per kg body weight have been ingested [25]. Lavage should be considered up to 12 hours post ingestion and should always be performed in the comatose patient [13,26]. Syrup of ipecacuanha must be used cautiously because of the risk for rapid onset of seizures and obtundation [27]. Induced emesis is preferred in children because it is less traumatic, but the patient must be conscious with an intact gag reflex.

Activated charcoal

Further reduction of absorption is promoted by administration of activated charcoal. Both in vitro and human volunteer experiments have shown that activated charcoal effectively adsorbs significant amounts of tricyclic antidepressants [28]. However, the clinical usefulness of charcoal has been questioned and several studies failed to show any benefit [29,30]. This may be explained by the fact that investigators used a small amount of charcoal only (10–20 g) and that several patients entered the study too late. Activated charcoal should be given in doses exceeding the ingested amount at least ten-fold and minimal instillation of 50 g in adults is recommended.

Elimination therapy

Forced diuresis, peritoneal dialysis, hemodialysis or hemoperfusion are of little value in the treatment since tricyclic antidepressants generally have a large volume of distribution and high lipid solubility as well as a high protein binding [31].

Plasma half-lives vary considerably between antidepressants, from 5 to 93 hours and may even vary for one specific agent such as amitriptyline from 9 to 50 hours, averaging 36 hours. However, some drugs are known to possess very long half-lives such as maprotiline, nortriptyline and protriptyline. Maprotiline in overdose has been shown clinically to produce a longer period of coma than most antidepressants [32].

Tricyclic antidepressants are metabolized in the liver by demethylation and hydroxylation. Metabolites are conjugated to inactive glucuronides which are then excreted by the kidneys [25]. A difference in liver blood flow will presumably affect the metabolism of antidepressants. However, critical symptoms of poisoning occur principally during the distribution phase ($t_{1/2}\alpha$) and to a minor degree during the elimination phase ($t_{1/2}\beta$) [24]. The distribution phase is not different in severe overdoses and it is unlikely to be changed by treatment with inotropic agents [33].

The degree of plasma protein binding is high for classical antidepressants, between 90 to 98%. New drugs have lower protein binding, namely 77% for fluvoxamine and 50% for moclobemide.

Supportive and symptomatic measures

Supportive and symptomatic measures are essential due to the relative inappropriateness of elimination therapy. All patients with a recent history of tricyclic antidepressant overdose should be observed for at least 6 hours post ingestion, in a medical facility [25]. Any patient with signs of major toxicity such as coma, hypotension, arrhythmias or QRS duration exceeding 100 msec should be admitted to an intensive care unit.

The level of consciousness, respiration and circulation should be monitored adequately. Laboratory and monitoring procedures upon admission should include electrocardiogram, plasma electrolytes, serial vital signs, respiratory and hemodynamic monitoring. An arterial line should be inserted and serial arterial blood gases should be checked.

As already mentioned, hypoxemia and acidosis should be prevented and counteracted enthusiastically. The development of acidosis, either respiratory or metabolic, increases the risk of arrhythmias and potentially worsens both hypotension and conduction delays [20,34]. Thorstrand [35] reported 31 out of 70 patients with blood pH <7.35 and 14 with blood pH <7.30. Several authors have reported severe acidosis by overdose with amoxapine [36–38]. Regular assessment of blood gases has been claimed to be as important as monitoring cardiac rhythm [39,40].

Sodium bicarbonate Sodium bicarbonate is the most widely advocated therapy for tricyclic antidepressant toxicity. The intravenous administration of sodium bicarbonate has proven effective in partially reversing prolongation of QRS duration and improving the hemodynamic performance [34,41]. Others have shown antiarrhythmic properties by sodium bicarbonate [42]. Brown [43–45] has shown that sodium bicarbonate is an effective antiarrhythmic agent in both experimental and clinical studies. The mode of action of sodium bicarbonate is somewhat unclear, and several mechanisms have been implicated. Brown [43] suggested that amitriptyline plasma protein binding increases as pH rises, thus reducing the unbound fraction. Nattel [46] suggested that the beneficial effect is largely due to alkalinization. Sasyniuk and Jhamandas [47,48] argued that the beneficial effects of sodium bicarbonate are related

to the reversal of the drug effects on phase 0 of the action potential and that this effect is due both to alkalinization and to increased extracellular sodium concentration. Pentel and Benowitz [34] found that sodium bicarbonate can partially reverse the cardiotoxic effects of antidepressants in animals with either normal or acidotic pH. They proposed the beneficial effects on QRS duration to be due to increased plasma sodium concentration and those on blood pressure to be due to additional factors, such as intravascular volume expansion. To summarize, sodium bicarbonate is an effective treatment and constitutes a well documented basis before any further intervention.

Physostigmine, a specific inhibitor of cholinesterase with both peripheral and central effects, has been proposed to reverse coma [49–52]. However, the risk of induction of bradycardia and triggering of convulsions should be considered. In one study of 43 cases of maprotiline poisonings, 6 out of 7 patients given physostigmine developed seizures [32]. The use of physostigmine is no longer recommended in the treatment of tricyclic antidepressant poisoning, at least not during the first six hours [53]. Afterwards, physostigmine might be helpful to reverse central anticholinergic symptoms.

Diazepam is useful when seizures develop. It has been used safely and extensively in tricyclic antidepressant poisonings. 5–10 mg are given intravenously or 10–20 mg orally. However, if the patient is breathing spontaneously, respiratory depression should be anticipated. In one experimental study by Follmer and Lum [54], diazepam pretreatment was highly effective in preventing both convulsions and death in cats suggesting that convulsions are an important factor contributing to lethality. In animal experiments, the reversal of diazepam effects by flumazenil, resulted in more frequent arrhythmias and increased mortality [55,56]. When diazepam fails to control seizures, approximately 500 mg of phenytoin may be given, if administrated slowly by intravenous infusion. Another possibility is chlomethiazole, but this drug may depress respiration and increase the secretion of mucous from bronchioli and should be reserved for patients on mechanical ventilation [13].

Intravenous fluids are primarily used to treat hypotension, a common finding in poisoning due to antidepressive agents. Persistent hypotension after administration of plasma volume expanders indicate a severe poisoning. Shannon et al. [57] found a 7-fold greater risk for developing life-threatening arrhythmias and a 3-fold greater risk of pulmonary oedema when compared to patients with normal blood pressure. Hypotension in tricyclic antidepressant poisoning is claimed to occur due to peripheral alpha-adrenergic receptor blockade with decreased systemic vascular resistance [58,59]. This effect on blood pressure seems to occur in mild to moderate poisonings and is even described as a side effect ("orthostatic hypotension") at therapeutic concentrations [60]. On the other hand, systemic vascular resistance increases in severe poisoning and hypotension is primarily caused by impaired myocardial contractility [57,61]. The augmented blood pressure associated with inotropic drugs may then reduce peripheral vascular resistance, even when using alpha-adrenergic stimulants such as norepinephrine or epinephrine [62].

Poisoning with tricylic antidepressants is associated with hypovolemia due to a generalized increase in microvascular permeability resulting in intravascular volume loss to the extravascular compartment. The primary aim of fluids is the return to a normal intravascular volume and serum osmolality [63]. The plasma volume is most effectively increased by colloid solutions [64]. Crystalloid solutions should be given simultaneously with colloids, but colloids increase plasma volume more than a comparable amount of crystalloids. Fluids must be administered with caution to hypotensive patients as pulmonary oedema appears to be more frequent in these patients [57]. Colloids increase oxygen delivery to a greater extent than crystalloids and the maintenance of a near-normal colloid osmotic pressure will reduce the fluid flux across a damaged alveolo-capillary membrane in the lungs minimizing the risk of pulmonary oedema [16,65]. In addition, hypertonic sodium solutions have been shown to be beneficial [66–68]. A sodium load increases heart contractility and the administration of 200–400 mmol of sodium lactate not only improves central hemodynamics but also shortens the QRS prolongation caused by tricyclic antidepressants on ECG [69,70], a reason why sodium lactate is often preferred to sodium bicarbonate, at least by French authors [67,68,71].

Treatment of arrhythmias and heart failure

Cardiac arrhythmias are multiple and variable in tricyclic antidepressant poisonings and include sinus tachycardia, premature ventricular beats, ventricular tachycardia, torsades de pointe, ventricular bradycardia and ventricular fibrillation. Arrhythmias appear as a consequence of autonomic effects as well as effects on the action potential of cardiac cells. A cholinergic blockade, a catecholamine excess in plasma, effects on depolarisation, repolarisation, automaticity and conductivity may be involved [72].

Treatment of arrhythmias is based on correction of hypoperfusion, hypoxemia, electrolyte disturbances and acidemia. Ström et al. [73] found severe hypokalemia in 27 out of 295 patients (9%) with potassium levels below 3.0 mmol/l. Thorstrand [35] found hypokalemia in 22 out of 153 patients (15%) with potassium levels below 3.6 mmol/l. Meredith and Vale [26] recommended maintenance of a high plasma potassium level around 4.5 mmol/l. Hyperkalemia was seemingly rare, found in one patient only in Thorstrand's study [35]; however, hyperkalemia may be associated with shock, hypoperfusion and metabolic acidosis.

Antiarrhythmic agents may still be needed after administration of sodium bicarbonate and the correction of acidosis and electrolyte disturbances. However, most antiarrhythmic agents exert membrane-stabilizing effects which may further reduce cardiac contractility so that their use is controversial [72]. A membrane-stabilizing effect, often referred to as quinidine-like, is directly depressant to the cardiac contractility in poisonings with tricyclic antidepressants. The membrane-stabilizing activity is a non-specific interaction between membrane lipid bilayers and the drug, resulting in depressed membrane excitability and reduced cardiac contractility [74] because of inhib-

ited fast-inward passive sodium current during depolarisation and action potential in excitable cells. Several antiarrhythmic agents, such as quinidine, disopyramide, procainamide, encainide and flecainide, exert effects on the cardiac conductivity system similar to those of tricylic antidepressants (e.g. prolongation of phase 0) and their use is therefore contraindicated. Other antiarrhythmic agents such as bretylium and amiodarone may induce torsades de pointe due to prolongation of the electrocardiographic JT interval. Antiarrhythmics classified as I-B according to Vaughan Williams, such as lidocaine and phenytoin, seem to be more useful as they do not slow conduction or depress cardiac contractility extensively.

(1) *β-adrenergic antagonists*. Tachyarrhythmias may be abolished with β-adrenergic antagonists, but in a study using dogs [48], they produced a profound and progressive hypotension leading to death. β-adrenergic antagonists also have a membrane-stabilizing effect with negative inotropic activity so that their use in poisonings with tricyclic antidepressants is no longer recommended. They have also been associated with hemodynamic instability and a pronounced fall in cardiac output in man [75].

(2) *Atropine*. Heart rate decreases after massive overdose and severe bradycardia may develop [76]. Atropine is of little value as antidepressants exert anticholinergic properties [72]. Cardiac pacing may be useful, but when cardiac contractility is severely depressed, pacing alone is unlikely to improve cardiac contractility or increase oxygen transport significantly [77].

(3) *Lidocaine*. Nattel [46] found lidocaine to be effective in reducing the rate of ventricular ectopic beats, although sodium bicarbonate had a greater and longer effect than lidocaine. In one experimental study by Brown using lidocaine in 4 poisoned dogs [44], 2 out of 4 improved. Human data supports the use of lidocaine, such as a study by Langou where the infusion of lidocaine was effective to control premature ventricular beats [78]. Others argue against the use of lidocaine claiming that its use should be discouraged because of resulting depressed cardiac contractility [25,79]. In any case, lidocaine should be administered cautiously because of the risk of precipitating seizures [72].

(4) *Phenytoin*. Phenytoin is another antiarrhythmic agent also used to control seizures that has been recommended in the treatment [80]. It is classified as type I b and does not prolong the action potential. However, rapid administration may induce hypotension, human data is restricted and phenytoin is not used routinely.

(5) *Magnesium sulfate*. Experimental data suggests that intravenous infusion of magnesium sulfate is effective against ventricular arrhythmias in antidepressant poisonings [81,82]. The mechanism of magnesium sulfate antiarrhythmic actions are unclear. Magnesium sulfate is known to decrease the resting membrane potential and decrease the tendency to abnormal impulse formation [83,84]. These effects have been suggested to be primarily mediated by increasing Mg^{2+} dependent Na^+ K^+ ATPase activity. Augmentation of Na^+ K^+ ATPase activity increases the intracellular potassium concentration and thus the membrane threshold potential [85]. Experience in humans is so far limited

but a few case reports indicate a possible role for magnesium sulfate, at least in arrhythmias characteristic of torsades de pointe [86,87]. Magnesium sulfate should not be used alone due to the risk of inducing severe hypotension.

Inotropic support. The choice of an inotropic agent in poisoning with antidepressants is somewhat controversial. Treatments with dopamine and dobutamine are generally accepted as first-line inotropic support. Antidepressants block the re-uptake of neurotransmitters, including norepinephrine and dopamine, by the presynaptic nerve terminus. Furthermore, poisonings with antidepressants are associated with increased catecholamine plasma levels which have been claimed to contribute to the development of arrhythmias [88,89]. When patients on therapeutic levels of antidepressants are given sympathomimetic agents such as epinephrine or norepinephrine, their vasopressor effect is expected to be potentiated and arrhythmias may occur [90]. Several authors advise against the use of any sympathomimetic agent, arguing that they may induce or worsen arrhythmias [72,91,92].

When further intervention is needed, limited human and experimental data is available. Several authors suggested that norepinephrine [25,62,93,94] as well as epinephrine [95–97] may be useful. In experimental studies, epinephrine and norepinephrine were shown to counteract many severe hemodynamic disorders induced by amitriptyline [61,82]. Both drugs increase cardiac output, myocardial contractility, blood pressure and heart rate with a major difference between both drugs, namely the higher blood pressure associated with norepinephrine treatment. Both epinephrine and norepinephrine are effective in improving cardiac performance and reducing mortality in severe TCA poisoning. Treatment with epinephrine was most effective in one experimental study and was not associated with an increased risk of arrhythmia or severe hypotension [61].

Monoclonal antibodies

Monoclonal antibodies specific of tricyclic antidepressants have been produced [98] and their use in animals has recently proved to decrease the toxicity of antidepressants. Sabouroud et al. [99] found a reduction of lethality in actively immunized rabbits. Pentel et al. [100] found a reduction in QRS-width in rats treated with antibodies against tricyclic antidepressants. They suggested that drug distribution was altered by increasing the efflux from the heart into the blood. Dart et al. [101] found in rats that the effectiveness of antibodies was dose-dependent. Hursting et al. [102] demonstrated that treatment with antibodies in rabbits induced significant changes in the absolute and relative concentrations of desipramine in both serum and urine. However, no human data yet exists and preliminary data indicate that a large amount of antibodies will be required, which will be difficult and expensive to produce.

Goals of treatment

The primary goal of therapy is obviously to initially increase the mean blood

pressure so that essential perfusion to the core circulation is maintained [65]. If allowed to continue, hypotension will result in hypoperfusion and oxygen debt and establish a vicious circle which could result in death. Hypoperfusion, metabolic acidosis and oxygen debt all accentuate the toxicity of tricyclic antidepressants, particularly their cardiotoxicity. Every effort must therefore be paid to increase oxygen delivery to vital organs and tissues and provide for the enhanced oxygen need of poisoned patients.

The physiological aims of treatment are the optimization of preload (left-ventricular end-diastolic volume), the decrease in afterload (systemic vascular resistance, SVR), the augmentation of myocardial contractility and the increase in oxygen delivery and consumption [100,101]. To fulfil these goals, the insertion of a Swan–Ganz catheter is essential in the critically-ill patient. Modern Swan–Ganz catheters will provide measurement of continuous mixed venous oxygen saturation, helpful in assessing the effects of any pharmacological intervention [62]. Another possibility is the use of transoesophageal echocardiography which is beneficial for judging myocardial ejection fraction and systolic and diastolic performance and will rapidly detect any improvement in the patient's health [102].

When cardiogenic shock develops despite the use of sympathomimetic drugs the insertion of an intra-aortic balloon pump may be helpful. Even extensive cardiac failure can be reversible in a relatively short period of time and the insertion of an intra-aortic balloon pump can be performed with the patient in bed at the intensive care unit [106,107]. Extra-corporeal circulation using a mechanical pump is another possibility for cardiac assistance that has been utilized successfully [108]. Prolonged resuscitation with closed chest massage has also been successful in poisonings even for a period of time exceeding 3 hours [109].

Discharge

As late complications are rare, patients should be maintained in hospital until they are fully awake, but a psychiatric and toxicological follow-up is requested in each case. Every patient should be observed for at least six hours, in general more, and normally overnight. Patients developing symptoms of severe poisoning should be kept in hospital longer. If the patient has an ECG with a QRS duration less than 100 msec and is fully awake he or she can be discharged provided psychiatric support is available [4,22].

NEW AGENTS

In the seventies, several antidepressants were introduced, for instance maprotiline, mianserin, nomifensine, trazodone, doxepin, lofepramine and amoxapine. They caused a significant proportion of casualties among antidepressant poisonings. Even more recently, several specific serotonin uptake

inhibitors have been introduced such as fluvoxamine, sertraline, citalopram and paroxetine. New monoamino-oxidase inhibitors are also available such as moclobemide. These new agents account for an increasing share of the market. Cardiac toxicity with these new agents is markedly lower than with typical tricyclic antidepressants such as amitriptyline, clomipramine or nortriptyline [110]. However, the prevalence of these new agents among suicide victims does not seem to be reduced [111].

Amoxapine

Amoxapine overdose has been associated with acute renal failure, lactic acidosis and an increased mortality rate [36–38,112]. In addition, amoxapine causes several acute and chronic untoward neurologic and endocrine reactions not commonly associated with the standard tricyclic agents.

Citalopram

Citalopram, another specific serotonin uptake inhibitor with weak anticholinergic and sedative effects, has been reported to cause very little cardiotoxicity [113].

Fluvoxamine

Fluvoxamine is a selective serotonin re-uptake inhibitor with low anticholinergic and sedative activity. It appears to have low toxicity in overdose [114]. There is one reported case of prolonged coma after ingestion of 5.5 g. Overdoses of up to 9 g produced minimal symptoms and led to full recovery. However, ventricular fibrillation due to fluvoxamine has been reported [115].

Moclobemide

Moclobemide is a short-acting, selective and reversible monoamine oxidase inhibitor, with few and mild side effects at therapeutic doses. In one study of 18 suicidal attempts, none developed serious heart events [116]. While pure moclobemide overdose seems benign, a combination with tricyclic antidepressants may result in serious poisoning even when moclobemide overdose is modest [111,117].

Nomifensine

Nomifensine was a potent dopaminergic and noradrenergic drug with low anticholinergic activity, and minimal cardiotoxicity and low morbidity/mortality in overdose [120]. It has been withdrawn from the market due to hemolytic anemias.

Paroxetine

Paroxetine, another specific serotonin uptake inhibitor with weak anticholinergic and no sedative effects, has reportedly lower cardiotoxicity in animal experiments than amitriptyline [118].

Sertraline

Sertraline, a selective serotonin re-uptake inhibitor, has presented with a favourable safety and toleration profile. Four cases of overdose were successfully managed with no significant sequelae or the need for intensive care [119].

Trazodone

Trazodone is a selective serotoninergic agent with low anticholinergic and some sedative activity. Serious cardiovascular and neurologic toxicity is rare with trazodone overdose [120].

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8. Anticonvulsants

INTRODUCTION

Epilepsy is a common condition with most studies indicating a prevalence of 0.5% [1,2]. Figures for lifetime prevalence are higher at 2–5% [2,3], indicating that approximately 1 in 50 people at some time will have 2 or more unprovoked epileptic seizures and will probably be treated with antiepileptic drugs.

Poisoning by anticonvulsants is not uncommon. In children accidental ingestion accounts for the majority of cases. In adults accidental intoxication may also occur and is most commonly iatrogenic [3,4]. Inappropriate dosage or dose increment prescribed by a physician unfamiliar with the drug's pharmacology or drug interactions may be responsible. Self-adjustment of dose by the patient or an alteration in drug pharmacokinetics due to intercurrent illness may also be a factor. Suicide attempts are commoner in patients with epilepsy [5,6] and this may be partly due to the higher incidence of personality disorder and psychiatric illness in this group of patients [7]. The anticonvulsants themselves may play a role, for example, the behavioural problems associated with phenobarbitone and the psychosis which has been reported with patients on vigabatrin [8]. Other risk factors identified in one study [9], include male sex, age 25–49 years, generalized tonic/clonic or complex partial seizures, long duration of disease, insufficient therapy, social difficulties and the availability of large amounts of antiepileptic drugs. Self poisoning has also been reported in the relatives of patients with epilepsy [4].

The pattern of prescribing in epilepsy is changing. The older anticonvulsants such as phenytoin and phenobarbitone with their narrow therapeutic range, worrisome toxic and adverse reactions and difficult pharmacokinetics are being used less commonly and being replaced by drugs such as carbamazepine and sodium valproate. In addition, the recent introduction of vigabatrin and lamotrigine has provided further options for physicians. In the future, therefore, we may expect to see more cases of poisoning by these later anticonvulsants and less of phenytoin and phenobarbitone. In the management of poisonings by anticonvulsants a major advance has been the introduction of multiple-dose activated charcoal. This has been shown to be effective with several of the anticonvulsants and although not without side effects itself [10–12], it appears to be safer than other methods of elimination enhancement.

PHENYTOIN

Phenytoin is a hydantoin derivative anticonvulsant. It is recommended for the management of all seizures except absence seizures. It is also used in the management of cardiac arrhythmias, particularly secondary to digoxin intoxication, trigeminal neuralgia and myotonia. It is available in tablet, capsule, oral suspension and injectable formulations. The usual adult maintenance dose is 300–400 mg daily aiming for a plasma concentration in the range 10–20 mg/l.

Pharmacokinetics

Phenytoin is slowly absorbed from the gastrointestinal tract, but bioavailability may vary amongst preparations from different manufacturers [13]. In oral overdose, absorption may be further delayed due to a reduction in gastrointestinal motility. Continued absorption for up to 2 weeks has been reported [14]. Given intramuscularly the drug crystallizes at the injection site and is absorbed slowly and erratically. Intravenous administration leads to peak levels within 10 minutes.

In plasma, phenytoin is approximately 90% bound, mostly to albumin. It is the concentration of free drug that is responsible for toxicity and therefore alterations in protein binding can markedly affect toxicity without affecting a change in total drug concentration (free drug concentration correlates more closely with clinical signs in overdose but is rarely measured). Approximately 5% of the drug is eliminated unchanged in the urine. The remainder is hydroxylated by the hepatic microsomal enzyme system mainly to the inactive metabolic 5-p-hydroxyphenyl-5-phenylhydantoin (HPPH). Metabolism of phenytoin may be decreased by drugs which inhibit these microsomal enzymes for example, cimetidine and fluconazole. HPPH excreted in the bile, undergoes enterohepatic circulation, is conjugated with glucuronide and is subsequently largely excreted in the urine. Elimination of phenytoin follows first-order kinetics at plasma concentrations <10 mg/l. At higher concentrations the kinetics approach zero order typical of a saturable enzyme system. At this stage further doses of drug may lead to large increases in plasma concentration.

Clinical features

Neurological signs. The clinical features of phenytoin intoxication are variable but predominantly affect the nervous system. Cerebellar dysfunction with nystagmus, ataxia and dysarthria is the commonest finding and usually resolves when plasma levels fall. There are, however, reports of cerebellar atrophy following acute phenytoin intoxication with residual cerebellar dysfunction [15,16]. Nystagmus is often the earliest sign and its absence is against the diagnosis of phenytoin toxicity. Other eye signs include slow saccades [17], ophthalmoplegia [18] and opsoclonus [19].

Phenytoin toxicity may affect the mental status of the patient resulting in lethargy, agitation or confusion. A comatose or totally unresponsive status is not typical of phenytoin intoxication. Uncommonly movement disorders may occur, in particular choreoathetosis [20–23], hyperkinesia [24], ballismus [25], orofacial dyskinesia [26], dystonia [27] asterixis [28], and myoclonus. Other neurological manifestations include tremor, hyper- or hyporeflexia, spasticity with clonus [29] and a reversible hemi/monoparesis [30]. An increase in seizure frequency has been reported to occur in some patients [31–33] which resolves when the phenytoin level falls into the therapeutic range.

Non-neurological signs. The commonest non-neurological manifestation of phenytoin intoxication is nausea and vomiting. Heartblock, bradyarrhythmias and hypotension are potentially fatal effects which may occur but are usually seen following intravenous administration. This may be due to overrapid infusion or insufficient dilution of the drug. It has been suggested that the propylene glycol diluent may be to blame. Oral intoxication very rarely results in cardiovascular morbidity. In one series of 57 patients with peak serum levels of 40 mg/l or more there were no cases of severe cardiovascular morbidity [34] and it is therefore not mandatory to manage stable patients with continuous ECG monitoring.

Other non-neurological manifestations reported include hypernatremic coma [35], hyperglycemic, hyperosmolar non ketotic coma [36] and priapism [37]. Death is a rare sequel to phenytoin intoxication although it has been reported following ingestion of 7500 mg of phenytoin [38].

Management

In cases of overdose, the patient should be protected from trauma if the ataxia is gross. The stomach should be emptied and activated charcoal given to prevent further absorption. As phenytoin is generally slowly absorbed both may be employed several hours after ingestion.

There is no specific antidote to phenytoin intoxication and most patients will recover with supportive measures only. Various methods to increase phenytoin elimination have been tried including forced diuresis, hemodialysis [39], peritoneal dialysis [40], exchange transfusion [41] and plasmaphoresis [42] but results have been disappointing. Charcoal hemoperfusion [43] may be of value in severe poisoning. More recently multiple dose activated charcoal has been shown to be of value [44–47]. This increases phenytoin elimination and is postulated to work by interrupting any enterohepatic circulation and by promoting movement of free drug from the blood into the bowel lumen.

Recovery from phenytoin poisoning may take several days because of the drugs saturable kinetics. In the patient with epilepsy, plasma levels should be monitored daily to help decide when to restart therapeutic doses and thus avoid withdrawal seizures.

CARBAMAZEPINE

Carbamazepine is an iminostilbene derivative structurally related to the tricyclic antidepressants. It is the anticonvulsant of choice for complex partial seizures and is used in most seizure types excluding absence seizures, myoclonic and akinetic seizures. It is used in the management of trigeminal and other neuralgias and less commonly in the management of some psychiatric disorders. It occurs in tablet and syrup formulations. There is no parenteral formulation. In epilepsy the usual maintenance dose is 600–1200 mg/day in divided doses, aiming for a plasma level in the range of 4–12.5 mg/l.

Pharmacokinetics

Carbamazepine is slowly and erratically absorbed from the gastrointestinal tract with peak levels attained in 6–24 hours. The drug is 70–80% bound to plasma proteins and is widely distributed throughout the body. Metabolism of carbamazepine occurs extensively in the liver with only 1–2% of the drug excreted unchanged in the urine. The major metabolite carbamazepine-10,11-epoxide is also pharmacologically active and may contribute to adverse effects. Because of its first-order non-saturable kinetics, carbamazepine is easier to use than phenytoin, and serious degrees of toxicity are therefore unusual in the routine therapy of epilepsy.

Clinical features

Cases of toxicity have been reported due to unforeseen interaction with other drugs [48–50], but the majority of cases of serious toxicity are due to deliberate self poisoning. The fatal dose is variable. Survival has been reported following ingestion of doses up to 80 g [51], although severe toxicity and death may result from cardiac failure or gastric aspiration at much lower doses [52,53]. Some studies have questioned the correlation between serum levels and the severity of the overdose [54]; however, in one study peak serum concentrations above 170 μmol/l were associated with an increased risk of serious complications [55].

Chronic intoxication with carbamazepine can affect many systems, but acute toxicity predominantly affects the nervous system. Anticholinergic effects similar to those of tricyclic antidepressants may also be prominent. The initial features are often cerebellar with nystagmus, ataxia, and dysarthria. At higher plasma levels, CNS depression may be the dominant feature. This may be associated with hyperreflexia, dilated pupils and sinus tachycardia. Seizure activity may be precipitated and is usually of tonic/clonic type. In severe cases, respiratory depression may require ventilation support. Other neurological effects include irritability [56], hallucinations [56], movement disorders such as choreoathetosis [56,57], myoclonus [58] and dystonias [59], opthalmoplegia [60], forme fruste neuroleptic malignant syndrome [61], and hyper- or hyporeflexia [62].

Cardiovascular abnormalities may also occur with carbamazepine intoxication [63]. Sinus tachycardia and hypotension are perhaps the commonest of these, but more serious complications such as prolonged PR, QRS, QT intervals [64], bradyarrhythmias and heart block [65] may occur. Other manifestations include acute pancreatitis [66], water retention with hypernatremia [67], hyponatremia [68], pulmonary oedema [69] and microhematuria [58].

Cyclical coma, that is, relapse after an apparent period of recovery, is a feature of carbamazepine overdose [56,64,70] and is thought to be due to the anticholinergic and central depressant effect of carbamazepine, resulting in a marked reduction of intestinal motility and protracted absorption. This situation may persist for up to 40 hours after which motility and absorption start to improve, with a resultant rise in plasma concentrations and recurrence of symptoms.

Management

The management of carbamazepine poisoning is largely supportive. The stomach should be emptied by ipecac-induced emesis or gastric lavage with endotracheal intubation if necessary. Rarely the drug may form concretions in the stomach which may need be removed by gastroscopic lavage or gastrotomy [71]. Charcoal decreases the absorption of carbamazepine and, because of the relatively slow absorption of the drug, may be effective several hours after the overdose [72]. ECG monitoring is mandatory for 24 hours because of the risk of cardiac arrhythmias. Convulsions if they occur, tend to be short lived and readily treated with benzodiazepines. Activated charcoal has been shown to enhance carbamazepine elimination in volunteers [72], and in cases of poisoning [73]. A recent study however has suggested that multiple doses are no more effective than 2–3 doses [74]. Charcoal hemoperfusion has also been shown to be of value [51,75,76] but is more invasive and should be reserved for the most severe cases. Plasmapheresis has also be used in extreme cases [77]. One case report has suggested that intravenous flumazenil may be of value in coma secondary to carbamazepine intoxication, possibly by decreasing intracerebral pressure [78]. Forced diuresis [79], peritoneal dialysis, and hemodialysis [80] have been shown to be of no benefit, probably because of the high protein binding of the drug.

SODIUM VALPROATE

Sodium valproate is a carboxylic acid derivative anticonvulsant used in the management of most seizure types including absence seizures. Sodium valproate is the sodium salt of valproic acid. In some countries valproate acid itself, or the magnesium salt may be available, but there are only minor pharmacokinetic differences in these preparations. Sodium valproate occurs in tablet, syrup, and liquid, parenteral preparations. The usual maintenance dose in an

adult is 0.6–2 g/day in divided doses and the usual therapeutic range is 40–100 mg/l; however, the therapeutic range of sodium valproate is only of very limited value as it correlates poorly with both therapeutic effects and adverse effects.

Clinical features

Intoxication with sodium valproate is usually due to deliberate self poisoning in adults or accidental ingestion in children. Less commonly it is the result of drug interaction [81]. Most poisonings tend to be benign and fatalities are rare. Two cases reported in the literature followed massive ingestion of valproate and death occurred as a complication of cardiorespiratory depression [82,83]. The clinical features correlate poorly with plasma concentrations [84]. Typically patients experience drowsiness and in acute intoxication this begins within a few hours of ingestion and may rapidly progress to coma in cases were more than 20 mg/kg have been ingested. This CNS depression may be complicated by cerebral oedema [85]. Other common features include nausea and vomiting, abdominal pain and diarrhoea. Elevation of liver enzymes may occur [86,87]. However, unlike chronic intoxication, acute overdosage usually causes only minor hepatic injury with resolution of enzyme abnormalities within 2 weeks. Thrombocytopenia and leucopenia [82] are also described. They may occur rapidly following acute intoxication but also resolve quickly. Less common neurological features reported include miosis [88], seizures [89], hypotonia [90], areflexia [91], tremor [92], myoclonic movements [58], hallucinations [89] and hyperactivity [89]. Cerebellar signs are not a typical feature. Other manifestations include hemorrhagic pancreatitis [82], elevated creatinine levels [87], acute renal failure [82,93], pyrexia of unknown origin [85,91,87] and metabolic abnormalities: hypoglycemia, hypocalcemia, hypophosphatemia, hypernatremia, metabolic acidosis [83,94].

Management

The management of acute sodium valproate toxicity is primarily supportive. The drug is rapidly absorbed and measures to empty the stomach and prevent further absorption are only of value if performed early. In addition to anticonvulsant properties, sodium valproate has been shown to have some morphine-like analgesic properties possibly related to increased GABA levels. Naloxone is known to reverse these actions and there are several reports of a rapid improvement in clinical condition following intravenous injection [88,95]. Methods to enhance elimination of sodium valproate have generally been of limited value. Combined hemodialysis/hemoperfusion may have a modest effect [87,93]. More recently, multiple doses of oral activated charcoal have been shown to increase clearance of sodium valproate despite the high protein binding [96–98] and we would recommend the use of this in all but the most minor intoxications. Overall the prognosis is good and recovery is usually complete. There is one report of persistent neurological sequelae following a

severe intoxication [91], however, it has been conceded that cerebral hypoxia could not be excluded as a factor.

PHENOBARBITONE

The incidence of barbiturate poisoning has been declining in recent years due to the increased use of other anticonvulsants. Phenobarbitone however continues to be widely prescribed. It is a long acting derivative of barbituric acid and is used in the management of both tonic/clonic and partial seizures. As a potent microsomal enzyme inducer, it is also used in the management of neonatal jaundice. The use of phenobarbitone is limited however by hypnotic side effects and the induction of paradoxical excitement and hyperactivity in children and the elderly. It occurs in tablet, elixir, and parenteral formulations. The usual maintenance dose in the adult is 60–180 mg/day usually taken at night, the usual plasma range in maintenance therapy being 10–40 mg/l.

Pharmacokinetics

Following oral administration absorption is virtually complete, but the rate of absorption may vary considerably. The drug is only about 40% protein bound and is widely distributed. About 25% of the drug is excreted unchanged with excretion enhanced by alkalinization of the urine. The elimination half life may be as long as 4–5 days.

Clinical features

The early signs of phenobarbitone poisoning, as with other anticonvulsants, are often cerebellar with nystagmus, dysarthria and ataxia. The severity of the poisoning correlates poorly with plasma concentrations. With increasing CNS depression, the patient becomes drowsy and progresses to coma. The coma in phenobarbitone poisoning is rarely deep and most patients respond purposefully to painful stimuli [99]. Only rarely is respiration sufficiently depressed to require artificial ventilation and usually occurs at serum levels greater than 100 mg/l. Hypoglycemia may complicate the neurological picture but is more commonly seen in poisoning with short acting barbiturates [100]. Hypothermia and hypotension are also more common with other barbiturates, but may occur [101,102]. Other features reported include bullous skin lesions [103,104], hypotonia and areflexia [100], reduced gastric motility and ileus, intestinal infarction [105], and the syndrome of inappropriate ADH secretion [106]. The diminished deep venous blood flow and temporary immobility in barbiturate coma may predispose to venous thromboembolism and pulmonary embolism [107]. The major cause of death in hospital is from pulmonary oedema and aspiration pneumonia [108] and can occur following acute ingestion of 2 g or more of phenobarbitone [99]. Recovery from phenobarbitone poisoning is very

slow because of the long elimination half-life. During the prolonged recovery phase behavioural disturbances are common [109] and the patient may prove difficult to manage.

Management

Absorption of phenobarbitone is often prolonged following acute intoxication because of delayed gastric motility. Measures to empty the stomach and limit further absorption should therefore be considered many hours after ingestion. Oral activated charcoal also limits absorption effectively [110]. In addition, multiple doses of oral activated charcoal has been shown to enhance elimination in volunteers [111] and in poisoned patients [112,113]. However, in a small controlled study, despite a significant increase in elimination of phenobarbitone, no clear effect was seen on clinical course [114].

Phenobarbitone is a weak organic acid and urinary excretion is therefore enhanced in an alkaline urine. Forced alkaline diuresis has been shown to increase elimination in phenobarbitone toxicity [115,116], but should be used with caution in the elderly and those with pre-existing cardiac or renal disease. The effect of treatment on phenobarbitone plasma concentrations, electrolytes and acid base status should be monitored. Some authorities believe that the technique can only be regarded as a safe treatment if carried out in a specialist unit where there is adequate experience, skill and biochemical support for its control [117]. Certainly activated charcoal is safer, easier to administer and probably as effective. The two methods of enhancing elimination are not mutually exclusive. For patients in deep grades of coma not responding to the above measures, other methods of enhancing elimination such as hemodialysis [118] or hemoperfusion should be employed.

PRIMIDONE

Primidone is a deoxybarbiturate anticonvulsant. It is used in most forms of epilepsy, except absence seizures, but is mainly a second-line drug. It is also used in the management of essential tremor. It occurs in tablet and suspension formulations. The usual maintenance dose in epilepsy is 500–1000 mg/day in divided doses. The therapeutic range is 5–12 mg/l.

Pharmacokinetics

Primidone is readily absorbed following oral administration and peak plasma concentrations are achieved 3–4 hours following ingestion. The degree of protein binding is low and the serum half life is 6–12 hours. About 40% of the drug is excreted unchanged in the urine. Primidone is extensively metabolized in the liver to phenylethylmalonamide (PEMA) and to phenobarbital. Both these metabolites have anticonvulsant action and may also contribute to

toxicity. However CNS depression appears to be due primarily to primidone itself and not its metabolites [119]. The half life of PEMA is 15 hours whilst that of phenobarbitone is much longer (50–150 hours).

Clinical features

The clinical features of primidone poisoning are of CNS depression with dysarthria, nystagmus and ataxia. Drowsiness, rarely progressing to coma, may also occur. The features of primidone poisoning overlap with phenobarbitone poisoning. Disinhibited behaviour may occur, but hypotension, hypothermia and respiratory depression are rare. One distinctive feature of primidone intoxication is the pressure of shimmering white crystals in the urine [120,121]. Primidone crystalluria is thought to be due to the low water solubility of primidone and occurs at plasma concentrations greater than 80 mg/l. There is some evidence that the crystals are nephrotoxic in vivo although severe renal failure has not been reported.

Management

The stomach should be emptied if more than 1 g has been ingested, but treatment is otherwise largely supportive. Vigorous hydration may augment elimination of unchanged primidone and lessen the propensity for crystal formation and possible nephrotoxicity. In severe cases hemoperfusion increases the clearance of primidone, PEMA, and phenobarbitone [121]. Multiple-dose activated charcoal may also be of value but as yet there are no clinical studies to confirm this.

ETHOSUXIMIDE

Ethosuximide is a succinimide derivative anticonvulsant used primarily in the management of absence seizure. The drug occurs in tablet and elixir formulations. The normal adult dose is usually 500–1500 mg/day and the plasma level required to control seizures is usually 40–100 mg/l. Ethosuximide is well absorbed following oral administration. Plasma protein binding is very low and the plasma half-life averages 40–60 hours. Approximately 20% of the drug is eliminated unchanged in the urine. The remainder is metabolized in the liver mainly to the inactive hydroxyethyl derivative which is excreted either free or in its conjugated form in the urine.

Ethosuximide is not used commonly in adults and cases of poisoning are rare. Dizziness and ataxia with CNS depression progressing to drowsiness and coma are the main features. Severe intoxication may cause respiratory depression. Nausea and vomiting may be an early feature.

Management of ethosuximide intoxication is mainly supportive. The stomach should be emptied if more than 1 g of drug has been ingested. Respiration

should be controlled if necessary by mechanical ventilation. In severe cases charcoal hemoperfusion may be of value [122].

VIGABATRIN

Vigabatrin is an anticonvulsant which became licensed for use in the United Kingdom in 1989. It acts by irreversibly inhibiting the enzyme GABA transaminase, inhibiting the breakdown of GABA and thereby increasing the concentration of the inhibitory neurotransmitter at the synapse. The drug has been used primarily as an adjunctive therapy in patients with refractory epilepsy but future investigation into its role as monotherapy is keenly awaited. It may also be used in the management of spasticity in conditions such as multiple sclerosis. The usual adult dose in epilepsy is 2–4 g/day.

Experience with vigabatrin is limited, but there appears to be only a low degree of toxicity with the drug. This may be related to the drug's mechanism of action. Once all the available GABA transaminase has been inhibited further drug will merely be excreted. In animal studies chronic intoxication has resulted in weight loss and chronic diarrhoea [123]. Of more concern is the presence of intramyelinic oedema (microvacuolation) in the brains of rats and dogs [123]. However this effect was reversible on stopping the drug and was not seen in 6 necropsies and 23 biopsy specimens taken from patients treated with vigabatrin for a mean of 25 months [124].

In 6 patients with acute vigabatrin intoxication (range 7.5–30 g) the clinical course was benign (Marion Merrell Dow Ltd, Personal Communication). Two patients developed behavioural disturbances with one developing a frank psychosis. Higher doses resulted in loss of consciousness. One patient developed myoclonic facial jerks. The patients were all treated conservatively and recovered without sequelae.

LAMOTRIGINE

Lamotrigine is a triazine anticonvulsant recently licensed for use in the United Kingdom [125]. It is currently used as an add-on therapy for patients with epilepsy refractory to other medications. It occurs in tablet formulation only. The usual maintenance dose is 200–400 mg daily in divided doses, but this is altered by concomitant administration of other antiepileptic drugs. Lamotrigine is well absorbed following oral administration and is 55% plasma protein bound. The drug is extensively metabolized in the liver and eliminated mainly in the urine as the glucuronide. The elimination half-life is approximately 29 hours.

There has been only one report of lamotrigine intoxication reported in the literature [126]. A 26-year-old male took 1350 mg of lamotrigine and developed a serum concentration of 17 mg/l 3 hours following ingestion. Clinical features

present included facial flushing, horizontal and vertical nystagmus, mild ataxia and hypertonia with brisk reflexes. ECG showed some widening of the QRS complex. He was treated with gastric lavage and oral activated charcoal and made an uneventful recovery. The elimination half life in this patient was 10 hours suggesting that oral activated charcoal was effective in increasing the clearance of lamotrigine. The ECG changes suggest an increased risk of arrythmia and ECG monitoring may be advisable.

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Human Toxicology, J. Descotes (Ed.)

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9. Drugs affecting the autonomic nervous system

The autonomic nervous system is divided into the sympathetic and parasympathetic nervous system. These two divisions are physiological antagonists and most organs are innervated by both. Drugs can interact directly with the receptor or with the release of the neurotransmitter, leading to the stimulation or the inhibition of the respective nerve and its action.

Despite the large number of compounds available for the inhibition or the stimulation of autonomic functions, the number of case reports of poisoning, not side effects, involving such substances is fairly limited with maybe the exception of drugs blocking β-adrenergic receptors. Furthermore, because most drugs can affect the autonomic nervous system to a certain extent and since this will be discussed at length in other chapters, this chapter will focus mainly on drugs that affect more specifically the autonomic nervous system.

DRUGS WITH SYMPATHETIC EFFECTS

Catecholamines, the neurotransmitters of the sympathomimetic nervous system, include epinephrine, dopamine, and norepinephrine. The adrenergic receptors are divided into two main types, α and β, depending on their response to catecholamines and adrenoreceptor blocking agents.

The toxic manifestations induced by overdoses of sympathomimetic drugs result from an accentuation of their pharmacological properties. Drugs that affect primarily the alpha-adrenergic receptors may induce mydriasis, vasoconstriction, coronary dilatation, bladder contraction, and decrease gastrointestinal motility. Physiological effects induced by β_1-adrenergic stimulation can include myosis, tachycardia, increased cardiac contractility, accelerated AV conduction, and renin release. Miosis, vasodilatation, bronchodilatation, hyperglycemia, decreased gastrointestinal motility, bladder relaxation, and renin release are physiological effects that can be noted following the stimulation of β_2-adrenergic receptors.

Epinephrine

Clinical Presentation. The administered doses of epinephrine depend on the reason for administration and vary between 1 to 3 μg/kg iv for anaphylactic reaction to 100 to 200 μg/kg for a cardiac arrest [1,2]. Epinephrine intoxication is essentially the result of administration errors. The toxicity of epinephrine varies with the dose administered and the route of administration. Indeed, for the same amount administered the subcutaneous route will induce less systemic effect than the intravenous route. However, there is a great range of inter-individual susceptibility and myocardial infarction has been reported in a patient following the administration of a usual dose of 0.3 mg subcutaneously for an anaphylactic reaction. The patient seemed to have developed a severe coronary vasospasm secondary to the epinephrine [3]. The minimal lethal dose reported is 3 to 4 mg sc or iv, but patients have survived doses up to 20 mg iv.

Increasing doses of epinephrine will induce the following symptoms: agitation, nausea, vomiting, abdominal pain, diaphoresis, palpitation, chest pain, hypertension followed by hypotension when the adrenaline is stopped, tachycardia, ventricular fibrillation, pulmonary edema, sub-arachnoid hemorraghies, and hemiplegia. Metabolic problems such as hypokalemia, hyperglycemia, and lactic acidosis are more frequently encountered with high doses of epinephrine intravenously (e.g. 2 mg in an adult) or following a continuous infusion [4]. Hypokalemia results from the stimulation of the Na-K ATPase which favors the entry of potassium into the cell [5].

Several factors are responsible for the hyperglycemia. First, the administration of epinephrine inhibits the secretion of insulin. Second, there is a diminution of the uptake of glucose by the peripheral tissue partly induced by the diminution of the secretion of insulin. Finally, there is an increase in glycogenolysis. Lactic acidosis is the result of tissue hypoxia secondary to vasoconstriction and an increase in oxygen consumption. The administration of high intravenous doses or accidental intra-aortic injection of epinephrine can cause vasospasm of the renal arteries leading to renal ischemia, oliguria and tubular necrosis [6].

In children, severe bradycardia with asystole has been reported following the accidental intravenous administration of racemic epinephrine [7]. In the newborn, Solomon et al. [8] have reported symptoms similar to those of a septic state following the accidental oral administration of racemic epinephrine. These newborns demonstrated clinical signs of shock such as pallor, diminished peripheral perfusion, and tachycardia but with a normal or elevated blood pressure. Furthermore, they could not tolerate food and exhibited signs of intestinal ileus. Radiography of the abdomen showed edematous and dilated intestine. Respiratory distress necessitating mechanical ventilation can occur in the following 24 hours. Laboratory tests demonstrated initially leucocytosis with neutrophilia and thrombocytosis that was followed 48 to 72 hours later by neutropenia and thrombocytopenia. One of these babies died and the autopsy showed erosions and an extensive necrosis of the gastrointestinal tract.

Treatment. Because of its short duration of action, most patients intoxicated with epinephrine do not require extensive treatment. The treatment is mainly symptomatic and agitation is usually controlled with benzodiazepine. Hypertension is usually transitory and, if asymptomatic, only requires observation of 4 to 6 hours. Severe hypertension can be treated with nifedipine or nitroprusside. Nitroglycerine could be used in patients exhibiting signs of coronary vasospasm with their hypertension. Propranolol should be avoided since it can increase the hypertension and cause pulmonary edema. Some authors [9] recommend low doses of labetalol (i.e. 5 mg iv). However, since the blocking effect on the α-receptors is approximately 7 times more important than on the α-receptors there is a residual stimulation of the α-receptors.

The treatment of hypotension follows the usual recommendations. First, administer fluids such as Ringer lactate or normal saline. If these maneuvers are insufficient start a dopamine perfusion followed by the administration of noradrenaline if necessary. Ventricular arrhythmias are treated with lidocaine. Pulmonary edema should be treated by the usual method and will substantially regress with the correction of the hypertension.

The accidental subcutaneous administration of epinephrine can induce severe tissular necrosis [10]. Furthermore, the accidental administration of epinephrine in regions such as the fingers or toes can cause serious tissular necrosis. In these instances the instillation of a solution containing lidocaine and phentolamine in the ischemic region can restore a normal circulation.

Dopamine and noradrenaline

Dopamine and noradrenaline overdoses induce symptoms similar to those cause by epinephrine intoxication: nausea, vomiting, headache, dyspnea, chest pain, tachycardia, arrhythmias. However, the risk of tissular necrosis secondary to vasoconstriction is greater with high doses of these agents because of their predominant effect on α-receptors. Indeed, reports of gangrene with these agents are not rare [11]. In susceptible patients (patients suffering from atherosclerosis, diabetes, and Raynaud's disease) tissular ischemia should be treated with phentolamine 5 to 10 mg iv.

Dopamine intoxication has been reported in a nurse who received accidentally two drops of non-diluted dopamine (40 mg/ml) in her eye. She developed systemic symptoms as well as ischemic manifestations on her electrocardiogram [12]. A newborn infant, having received a perfusion of 358 μg/kg/minute of noradrenaline for 35 minutes, presented with minor symptoms. His skin was gray, the capillary filling was absent, and his blood pressure measured in the umbilical artery was 100/70 mmHg [13]. The symptoms disappeared with the administration of nitroprusside (0.025 μg/kg/min iv).

Dobutamine

Both hypertension and hypotension have been reported following the acci-

dental administration of high doses of dobutamine [14,15]. The hypotension resulted from the reduction of peripheral vascular resistance secondary to a stimulation of β_2-receptors. Despite a predominant β_1-effect, dobutamine can cause tissue necrosis if accidentally injected subcutaneously [16].

Isoproterenol

Palpitations, angina, tachyarrhythmias, myocardial ischemia or necrosis, as well as a severe hypotension with warm extremities can be encountered with high doses of isoproterenol. The treatment of choice for hypotension induced by isoproterenol is propranolol (bolus of 1 mg iv to a maximum dose of 10 mg) [17].

Salbutamol and terbutaline

Salbutamol and terbutaline intoxications have occurred following oral overdoses or accidental subcutaneous injections [18–20]. Patients developed chest pain, agitation, tremors, tachycardia, palpitation, and occasional extra systoles. One patient exhibited low blood pressure (i.e. 90/60 mmHg) [19]. Electrocardiogram changes included sinus tachycardia in all patients with ST segment depression and inverted T waves in one patient [20]. All these changes reverted to normal within two days. In addition, hypokalemia and elevated glycemia have also been reported [18].

Patients with β_2-adrenergic agonist overdoses presenting to the hospital within one hour of the ingestion should undergo gastric evacuation by ipecac syrup induced vomiting if alert, or by orogastric lavage if obtunded. All patients having ingested a toxic dose of β-adrenergic antagonist agents should receive activated charcoal orally or via a gastric tube. Since the optimal dose of charcoal is not clearly established, the largest amount tolerated by the patient should be given. Usually this amounts to approximately 1 g/kg. Activated charcoal should be given every 3 to 4 hours until charcoal stools are produced. Cathartics such as sorbitol or magnesium citrate, should be given only with every other dose.

Most patients with β_2-adrenergic receptor agonist poisoning do not require treatment for their sinus tachycardia. Ten milligrams of propranolol at a rate of 1 mg every three minutes have reduced the heart rate of a patient intoxicated with salbutamol [18]. Hypokalemia and hyperglycemia usually do not require any treatment.

Ergot alkaloids

The ergot alkaloids are natural or semisynthetic compounds derived from ergot. The primary clinical uses of the ergot alkaloids have been to relieve pain from migraine and to contract the post-partum uterus. The pharmacological effects of the ergot alkaloids appear to result primarily from their capacity to act as partial agonists and antagonists to α-adrenergic, dopamine and serotonin receptors. The central effects of ergotamine are probably mediated

through dopamine mechanisms and include both stimulation and inhibition. Agonistic effects may appear at doses lower than those required to produce antagonistic effects. Mydriasis, hyperthermia, and vomiting are signs of central stimulation. Inhibition of the vasomotor and baroreceptor centers produces vasodilation, hypotension and bradycardia. The peripheral effects of ergotamine include uterine contraction and vasoconstriction of both arteries and veins. This peripheral vasoconstriction may elevate the blood pressure and reduce the blood flow through various organs or extremities. Very high doses of ergotamine may induce adrenergic blockade resulting in hypotension, reflex tachycardia, miosis, and central nervous system depression.

Clinical presentation. Toxicity from ergot alkaloids generally manifests as focal or generalized arterial spasm with signs and symptoms of organ or extremity ischemia. Although tachycardia is frequently noted, bradycardia can also occur and may be associated with either hypertension or hypotension. Prolonged vasoconstriction will lead to pain, pallor, coolness, paresthesias, pulselessness and in severe cases, even the development of gangrene in the extremities [21,22]. Atrial fibrillation, ventricular fibrillation and asystole have been reported with an ergotamine overdose [23]. Central nervous system manifestations noted with ergotamine poisonings have included, headache, lethargy, coma and seizures [21,24]. Chronic poisoning may result in confusion and focal neurological deficits that are usually reversible but may require days to weeks for resolution [25]. Psychotic disturbances and mental instability have also been noted after an overdose of ergot alkaloids [22]. Vomiting accompanied by abdominal cramps and diarrhea as well as ischemic pancreatitis and hepatitis can occur with ergotamine poisonings [26]. Renal toxic manifestations have included flank pain, hematuria, oliguria and azotemia [23,27]. Signs and symptoms usually begin within 4 hours of ingestion. However, symptoms of ischemia may be delayed 12 to 24 hours following an acute overdose. The duration of effects is variable. Arterial spasms may persist for as long as 3 days and ischemic neurological deficits may be permanent or slowly resolve over a period of days to months. The acute toxic dose of ergotamine is not clearly established. A child survived after having ingested a dose of 15 mg of ergotamine, while a dose of 12 mg was fatal in another patient [27].

Treatment. The diagnosis and treatment of ergot alkaloids poisoning is based on clinical findings. Measures to evacuate the gastric content (i.e. ipecac induced emesis or gastric lavage) following significant oral overdoses of ergot alkaloids should be initiated within an hour of the ingestion. In other cases patients should receive activated charcoal. The optimal dose of charcoal is not clearly established, therefore, the largest amount tolerated by the patient should be given. Usually it amounts to approximately 1 g/kg. Activated charcoal should be given every 3 to 4 hours until charcoal stools are produced. Cathartics such as sorbitol or magnesium citrate, should be given only with every other dose. The efficacy of repeated administration of charcoal with or without cathartics have not been firmly established. Activated charcoal should be avoided if an ileus occurs.

Vasospasms have been treated supportively, pharmacologically and surgically with various success. Intravenous infusion of sodium nitroprusside have been successful in reversing ergotamine-induced vasospasm [28–30]. Nitroprusside was started at a rate of 25 to 50 μg/min and gradually increased to a maximum of 300 μg/min until the cyanosis disappeared and pulses, warmth, and blood pressure returned to the affected limb. The infusions were continued for 9 to 36 hours and then tapered. Arterial infusions of sodium nitroprusside were used in a patient unresponsive to intravenous sodium nitroprusside [31]. In less severe cases nifedipine (10 mg orally three times a day) and captopril (50 mg orally three times a day) were effective in reversing signs of peripheral ischemia [32,33]. Hyperbaric oxygen treatment has been successful in reversing ergotamine-induced peripheral ischemia when other measures have failed [34]. Kinetic data do not support the use of forced diuresis, peritoneal dialysis, hemodialysis or hemoperfusion in the treatment of ergot alkaloid poisonings.

DRUGS WITH SYMPATHOLYTIC EFFECTS

The toxic manifestations induced by adrenergic receptor antagonist overdoses result from an accentuation of their pharmacological properties. The blockade of α-adrenergic receptors may induce miosis, postural hypotension, reflex tachycardia, angina, and gastric hyperacidity. Hypotension, cardiac arrhythmias, bradycardia, pulmonary edema, and hyperkalemia may be noted following the blockade of β_1-adrenergic receptors. The physiological effects that can be observed with β_2-adrenergic receptors blockade may include hypertension, bronchospasm, Raynaud's phenomenon, hypoglycemia and hyperkalemia.

Drugs blocking β-adrenergic receptors

Clinical presentation. In general, β-blocking agents affect primarily the cardiovascular and central nervous systems as shown in Table 9.1.

In overdose, β-blockers lose their specificity and both β_1 and β_2 receptors are blocked, resulting in a decrease in the heart rate, myocardial contractility, cardiac output and conduction velocity. In addition, the membrane-stabilizing activity of drugs like propranolol, oxprenolol, and alprenolol as well as the direct myocardial depressant effect of β-blockers at high doses will contribute further to decrease the myocardial contractility. As a result, the hypotension noted following β-blocker overdoses is due mainly to a decrease in the cardiac output and partly to a decrease in the heart rate. Almost all β-adrenergic antagonists will induce hypotension following large overdoses [35–44].

Severe bradycardia is common with propranolol poisoning [35] and has also been reported with oxprenolol [45], and alprenolol [46]. Although bradycardia seems to occur more frequently with agents having membrane depressant actions, it has been reported with other β-adrenergic antagonists such as acebutol [47] and atenolol [48–51]. Progressive heart block is frequent with

Drugs	Pulse	Blood pressure	Coma	Seizures	Respiratory arrest	Death
Acebutol	↓	↓	+			+
Alprenolol	↓	↓	+			+
Atenolol	↔,↓	↑,↓	+			
Labetalol	↔	↓				
Metoprolol	↔,↓	↓	+	+		+
Nadolol	↔,↓	↓	+			
Oxprenolol	↓	↓	+	+	+	+
Pindolol	↑[1]	↔,↑	+			
Propranolol	↓[2]	↓	+	+	+	+
Sotalol	↓[3]	↓				+

[1]Sinus tachycardia, hypertension.
[2]Rarely ventricular fibrillation, QRS widening.
[3]Ventricular arrhythmias, QT prolongation.

Table 9.1. *Main toxic effects of* β*-blockers*

propranolol poisoning, but not with other β-adrenergic antagonists lacking membrane depressant activity. The partial sympathomimetic action of pindolol and practolol is possibly responsible for the tachycardia and hypertension encountered occasionally following intoxication with these agents [35,51]. The heart rate may remain within the normal range with nadolol, labetalol and metoprolol overdoses even when hypotension is present [36–40].

Sotalol possesses class III antiarrhythmic actions such as the capacity to prolong the cardiac potential and hence the QT interval of the electrocardiograph but lacks membrane depressant action and intrinsic sympathomimetic activity. Following massive overdoses, patients will present with bradycardia and may develop multifocal ventricular extra systoles, paroxysmal ventricular tachycardia, and ventricular fibrillation [41–43]. The ECG will show a prolongation of the QT interval in significant sotalol poisonings. The exact mechanism responsible for neurological manifestations is not known. Lipophilic drugs with membrane stabilizing activity such as propranolol and oxprenolol are more likely to induce seizures and rapid loss of consciousness than agents lacking these properties [35,44].

Because of the small number of cases of β-blocker intoxications reported in the literature, it is impossible to determine definitively a toxic dose in humans. Furthermore, toxic doses seem to vary greatly. For example, one patient died after having ingested 3.2 g of sotalol while another patient survived after having ingested 8 g. Obviously, patients' susceptibility to β-blockers will vary. Patients with myocardial disease may develop signs of serious toxicity at lower β-blocker blood concentrations than patients with a normal heart. Therefore, a prudent approach to consider would be that any patient who has ingested more than 3 to 5 times the recommended therapeutic daily dose is at risk of developing signs of toxicity.

Following an acute overdose, signs and symptoms usually occur within 1 to 2 hours after the ingestion. The duration of symptoms following β-blocker intoxications cannot be estimated based on their pharmacokinetic data; signs of toxicity have lasted for more than 72 hours in some cases [35]. Laboratory abnormalities are mainly electrocardiographic alterations and rarely hypoglycemia. Electrocardiographic changes include first degree atrioventricular heart block and sinus bradycardia. Massive intoxications induce disappearance of P waves, intraventricular conduction defects, and asystole. Drugs with membrane stabilizing activity like propranolol, may induce a widening of the QRS complex. Significant sotalol poisoning will induce a prolongation of the QT. The determination of plasma concentrations of β-adrenergic receptor antagonists is not useful. It is impossible to establish a correlation between the amount ingested, the plasma concentration and the severity of an intoxication. In addition, decisions regarding treatment rely on the clinical status regardless of plasma concentrations.

Treatment. As for all emergency situations, maintain the patient's airway and assist ventilation if needed. Glucagon, with its inotropic effect independent of the β-receptors, has been the most effective drug in the treatment of hypotension secondary to β-blocker intoxications and is considered the drug of choice [37,40,44,51]. The ideal dose has not been established, but in adults 1 to 3 bolus doses of 10 mg followed by infusion of 1 to 2 mg/hour have been used. If this treatment is ineffective adrenaline has been reported to improve heart rate and blood pressure in β-blocker poisonings. Initial doses of 10 to 30 μg/min have been recommended [51]. Large doses of isoproterenol (800 μg/min) were needed to obtain a good response in propranolol poisoning [52], whereas smaller doses were proven to be ineffective [53]. The efficacy of dopamine and dobutamine in β-blocker poisonings remains questionable [40,44,51,54]. Atropine (0.01–0.02 mg/kg iv) is the most frequently used agent for bradycardia but it seems the least effective [51]. In patients with severe overdoses, an endovenous pacemaker may be required and intra-aortic balloon pump has also been used successfully in a massive propranolol overdose [54,55]. Prenalterol, a cardioselective β-adrenergic receptor agonist, has been used successfully in β-blocker poisonings. Intravenous bolus doses of 5 to 10 mg followed by 5 mg/hour infusion are recommended [51]. A total dose of 420 mg given over a 24-hour period was needed in a massive metoprolol overdose [56]. Ventricular tachycardia and fibrillation following sotalol intoxication may benefit from infusion of lidocaine.

Seizures have been controlled effectively with diazepam. If necessary, phenytoin (15 mg/kg iv over 20 to 30 minutes) and phenobarbital (15–20 mg/kg iv over 20 to 30 minutes) should be added. Hypoglycemia can be treated with glucose and glucagon. If there is evidence of bronchoconstriction, β_2-agonist agents and aminophylline should be administered.

Measures to remove the gastric content should probably be carried out only in patients present in the emergency room less than an hour after their overdoses. The gastric content can be removed using induced emesis with syrup of ipecac in alert patients or by gastric lavage in obtunded patients provided

that their airways are protected. Gastric lavage efficacy greatly improves when performed with a large-bore tube. All patients having ingested a toxic dose of β-adrenergic antagonist agents should receive activated charcoal orally or via a gastric tube. The optimal dose of charcoal is not clearly established, therefore, the largest amount tolerated by the patient should be given. Usually it amounts to approximately 1 g/kg. Activated charcoal should be given every 3 to 4 hours until charcoal stools are produced. Cathartics such as sorbitol or magnesium citrate, should be given only with every other dose. The efficacy of repeated administration of charcoal with or without cathartics has not been firmly established. Activated charcoal should be avoided if an ileus occurs.

Forced diuresis is not indicated in β-blocker intoxications. The efficacy of hemodialysis and hemoperfusion have never been evaluated in the treatment of β-blocker intoxications, but based on their pharmacokinetic data these techniques would not be effective and are not recommended.

DRUGS WITH CHOLINERGIC EFFECTS

Parasympathomimetic agents are cholinergic agonists that affect acetylcholine at the somatic neuromuscular junction, all autonomic ganglia, adrenal medulla, central nervous system and all postganglionic parasympathomimetic fibers. Cholinergic receptors are divided into muscarinic and nicotinic receptors. Parasympathomimetic agents vary in selectivity for muscarinic and nicotinic effects. Typical symptoms of muscarinic stimulation include myosis, flushing, bradycardia, bronchospasm, increases bronchosecretion, involuntary urination and/or defecation, sweating, lacrimation, and vasodilatation. Some agents will affect the neuromuscular junction producing nicotinic effects such as muscle cramps, fasciculation, weakness, and paralysis.

Carbachol

One patient poisoned with carbachol pills presented to the emergency room with nausea, abdominal cramps, explosive defecation, salivation and transpiration one hour after the ingestion. At his arrival he was somnolent, with an heart rate of 10 to 15 beats per minute, blood pressure was 100/35 mmHg, temperature 35°C, and his pupils were pinpointed with no reaction to light. The ECG showed an extreme sinus bradycardia, rate 30 beats/min., with AV block. With the administration of isoprenaline his heart rate increased to 40 beats/min and the ECG showed a second degree AV block type Mobitz 1 with the Wenckenbach phenomenon. The toxic amount of carbachol ingested by the patient was 30 to 40 mg. A child died after being given 1 mg/kg of carbachol [57,58].

Pilocarpine

A 39-year-old adult was inadvertently injected subcutaneously into the right deltoid area with 2 ml of 4% pilocarpine (a total of 80 mg of pilocarpine). She

sweated profusely, hypersalivated, and became nauseated. Later she developed dry mouth and chills. Her breathing was labored, and she felt as though her lungs were congested. She urinated 6 to 8 times and had 3 to 4 watery bowel movements over a six hours time period. Symptoms slowly abated over four days [59].

Pyridostigmine

Pyridostigmine bromide is a reversible cholinesterase inhibitor. Accumulation of acetylcholine at the cholinergic synapses results in symptoms and signs of cholinergic hyperactivity. Pyridostigmine is used for the treatment of myasthenia gravis and for reversing nondepolarizing neuromuscular blockade. It has also being recommended for pretreatment against intoxication with organophosphorus nerve agents. Patients having ingested doses ranging from 390 to 900 mg developed the following symptoms: emesis, abdominal pain, diarrhea, hypersalivation, urinary incontinence, blurred vision, fasciculations and muscle weakness [60]. No CNS manifestations were exhibited by these patients.

Pyridostigmine is poorly (bioavailability: 5–10%) but rapidly absorbed from the gastrointestinal tract. Symptoms develop within 15 minutes to 2 hours and lasted for several hours. The elimination half-life time is 3 to 4 hours. The diagnosis can be confirmed by determining the patient's serum cholinesterase activity. However, the interpretation of a single post-exposure value is made difficult by the wide range in normal cholinesterase activity. Atropine antagonizes the cholinergic effects by blocking the muscarinic receptors. In cases of moderate pyridostigmine poisoning, one to four doses of atropine (2.0 mg iv) is usually sufficient [60].

Nicotine

Nicotine is well absorbed via inhalation, dermal or rectal exposure. The oral absorption of nicotine from cigarettes or cigars is usually incomplete. With the introduction of nicotine patches and gums the frequency of these intoxications may increase in the future.

Clinical presentation. Symptoms following a nicotine intoxication from chewing gum usually begin within 15 to 20 minutes of the ingestion in children [61]. The patient may present with nausea, vomiting, abdominal pain, and increased salivation. Vomiting usually occurs before other toxic effects and its incidence varies from 16.4 to 63.2% [61,62]. Other effects such as confusion, agitation and restlessness are followed by lethargy, convulsions, and coma following severe poisoning [63].

Cardiovascular manifestations include hypertension followed by hypotension and several types of arrhythmias such as atrial and ventricular fibrillation [63,64]. In large doses, nicotine can induce respiratory failure and death [65]. The duration of symptoms is about 1 to 2 hours following a mild exposure, and up to 18 to 24 hours following a severe intoxication.

Treatment. Spontaneous vomiting usually occurs after significant exposure with cholinergic agonist agents. Therefore, induced emesis is probably not indicated. Gastric lavage with a large bore orogastric tube (in an adult 36 to 42 French) may be indicated if performed soon after the ingestion (less than one hour) or in patients who are comatose or at risk of developing seizures. As for all other intoxications, activated charcoal should be administered following potentially severe cholinergic intoxications. The optimum dose of activated charcoal is not established, however, it is usually recommended to give between 50 to 100 g in an adult or approximately 1 g/kg.

There is no information regarding the effectiveness of forced diuresis, hemodialysis and hemoperfusion following an intoxication with cholinergic agents. Therefore, pending such studies none of these therapies are recommended following an acute overdose with cholinergic agents. Atropine sulfate is the drug of choice to reverse the action at the muscarinic receptor. The initial dose in an adult is 2 mg intravenously repeated every 5 to 60 minutes as needed to control muscarinic symptoms [60]. Epinephrine may assist in overcoming severe cardiovascular or symptoms of bronchospasm. If seizures cannot be controlled with diazepam or recur, phenytoin or phenobarbital can be used.

DRUGS WITH ANTICHOLINERGIC EFFECTS

Parasympatholytic agents block cholinergic effects. The physiological effects encountered following an overdose may include mydriasis, decrease bowel movements, elevated blood pressure and temperature, erythema, dry skin, delirium , tachycardia, and urinary retention.

Atropine and scopolamine

Clinical presentation. The manifestation following an acute overdose will usually start within an hour of the ingestion [66,67]. The patient may very often be quiet and sedated in the first hours of the intoxication, however, as time passes they may become increasingly restless with uncoordinated movements and hallucinations [66].

Because of the small number of cases of anticholinergic drug intoxications reported in the literature it is impossible to determine with certainty a toxic dose in humans. The range of toxicity is unpredictable and varies greatly depending on the products. Children have exhibited toxic manifestations after ingesting doses of 3.2 mg/kg to 20 mg/kg of atropine while others have tolerated high doses of atropine following accidental injections with automatic atropine injectors [66,68,69]. Furthermore, other factors such as the age of the patient, the patient's health status prior the incident, or the concomitant ingestion of other drugs, can influence the patient outcome. Therefore, a prudent approach would be to consider that any patient who has received more than 3 to 5 times the recommended therapeutic daily dose is at risk of developing signs of toxicity.

An intoxication with anticholinergic agents can occur following: the installation of eye drops [70,71], the ingestion of an overdose orally [66,68,72] or by injections of high doses of anticholinergic agent [69,73]. Anticholinergic poisoning has also occurred in patients as well as respiratory therapists who were exposed to anticholinergic agents via aerosol administration. An adult man, who received two nebulized doses of 0.5 mg of atropine, developed headache, blindness, confusion and disorientation shortly after the second dose [74]. One patient developed scopolamine poisoning after having sniffed adulterated cocaine [75].

The anticholinergic syndrome is characterized by the following symptoms: dry mouth, warm red skin, dilated pupils, hallucinations, tachycardia, diminished bowel movements, and urinary retention.

The CNS toxic effects of anticholinergic agents include anxiety, altered mental status, delirium, disorientation, hallucination, hyperactivity and seizure. Severe poisonings may also induce coma, medullary paralysis and death [76–78]. Classically it was thought that atropine would cause CNS excitation and scopolamine CNS depression. However, recent cases have shown that large doses of scopolamine may produce excitation similar to that of atropine [67,75]. Acute hypothermia has been reported following a total dose of 0.8 mg of atropine given intravenously to a young boy [79]. The peripheral toxicity of anticholinergic agents on the cardiovascular system is characterized by tachycardia, usually sinus tachycardia and sometimes hypertension [72].

A 26-year-old woman seven months into her pregnancy was injected by error with 75 mg of atropine. She developed mental confusion with excitation tachycardia, increased body temperature, and mydriasis. She was hospitalized for 3 days and was given prostigmine. She had a normal delivery a few weeks later and her child was normal [73]. Scopolamine readily crosses the placenta. A newborn child, whose mother received multiple doses of scopolamine (total dose: 1.8 mg) during labor, exhibited signs of anticholinergic poisoning: temperature of 100.4°F, pulse rate of 200 beats/min, lethargic and somewhat barrel chested. Fifteen minutes after receiving 0.1 mg of physostigmine IM, her heart rate was down to 140, her chest was no longer barreled, her activity increased, the fever subsided during the next several hours and there were no further problems [80].

The duration of toxic signs and symptoms may vary from hours to even days. In most patients, toxic manifestations such as urinary retention, decrease of peristaltism, tachycardia, agitation, and hallucinations improve within 48 hours while mydriasis frequently lasts up to a week following atropine overdose [66]. Anticholinergic agents can be measured in the blood or urine. However, there is no correlation between blood concentration and pharmacological or toxicological effects. For example, in a study of 248 children who accidentally injected themselves with personal automatic injectors [69], serum atropine concentrations ranged from 7.5 to 69 ng/ml. Therefore, since anticholinergic poisoning is of rapid onset and is usually easily recognizable, clinical judgment seems to be more important that the determination of blood concentrations.

Treatment. Anticholinergic agents slow gastrointestinal motility and sustained release preparations are available. Theoretically, gastric emptying could be successful even if the patient arrives several hours after the ingestion to the emergency room. However, no studies have evaluated how long after the ingestion of anticholinergic agents such procedures should be carried out. Therefore, based on our current knowledge about the efficacy of gastric emptying methods, such procedures should be carried out only if the patient is in the emergency room less than an hour after the ingestion of the drug. The gastric content can be removed using induced emesis with syrup of ipecac or by gastric lavage. Gastric lavage is efficacious only if it is conducted with a large bored tube. All patients who have ingested a toxic dose of anticholinergic agents should receive activated charcoal orally or via gastric tube. The optimal dose of charcoal is not clearly established. Therefore, the largest amount tolerated by the patient should be given, which usually amounts to approximately 1 g/kg. Multiple dose activated charcoal, given every 3 to 4 hours, may enhance total body clearance and elimination due to decreased gastrointestinal motility. Cathartics such as sorbitol or magnesium citrate, should be given with every other dose of charcoal until charcoal stools are produced. However, the safety and efficacy of repeated administration of charcoal with or without cathartics have not been firmly established. Activated charcoal should be avoided if an ileus secondary to anticholinergic effect occurs.

The majority of anticholinergic drugs are mainly metabolized in the liver and only their inactive metabolites are eliminated by the kidney. Therefore, forced diuresis is not useful. Furthermore, most of these drugs have a large volume of distribution. Therefore, dialysis techniques such as peritoneal or hemodialysis as well as hemoperfusion are not useful. Physostigmine, a cholinergic agent, is recommended to reverse severe anticholinergic effects. Indications for its use include: intractable seizure, severe hallucination, severe hypertension or arrhythmias which do not respond to other antihypertensive or antiarrhythmic medications [71,75,77,78,80]. Although coma may reverse dramatically in some cases, physostigmine should not be used just to keep a patient awake as the risk of causing serious cholinergic toxic effects far outweigh this benefit [67]. These side effects include hypotension, bradyarrhythmias, asystole and seizures. Other relative contraindications to its use include: asthma, gangrene, cardiac conduction delays, mechanical obstruction of the gastrointestinal tract or urogenital tract. In adults, 0.5 to 2.0 mg of physotigmine may be given by intravenous infusion over 5 minutes. This dose may be repeated every 40 to 60 minutes until reversal of symptoms. In children 0.02 mg/kg, up to a total single dose of 0.5 mg, may be given over 5 minutes. If toxic effects persist and no cholinergic effects are produced, then physostigmine may be re administered at 5 min-intervals until a maximum dose of 2.0 mg is given.

Repeated doses of 5 to 10 mg of diazepam have been used successfully to control severe agitation and hallucination in three children intoxicated with atropine [66]. Seven milligrams of haloperidol was given to sedate a severely

agitated patient intoxicated with scopolamine [78]. Supraventricular arrhythmias do not require treatment unless they induce cardiovascular instability. Physotigmine administration reduces cardiac rhythm and blood pressure.

Diphenoxylate-atropine

Diphenoxylate-atropine is a common antidiarrheal product containing 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate per tablet or 5 ml of liquid. This agent is frequently encountered in pediatric overdoses and more than 100 cases have been reported in children [81]. Classically, diphenoxylate-atropine poisoning manifestations were described as occurring in two stages. The first stage, lasting two or three hours, was that of atropine toxicity. Flushing, lethargy, hyperpyrexia, convulsions, tachypnea, mydriatic pupils poorly responding to light, and/or hypotonic reflexes could be noted. The second or diphenoxylate stage included some or all of the following toxic manifestations: hypothermia, myosis, spasticity, paralytic ileus, muscular twitching, urinary retention, pulmonary edema, severe respiratory depression, coma, and respiratory arrest [82]. This stage could occur abruptly or as long as 36 hours after the ingestion. However, small children intoxicated with Lomotil® do not always have signs of atropinism followed in a few hours by signs of opioid overdose. Of 36 cases, only 4 patients (11%) showed this pattern. Twenty-one patients (58%) had atropine symptoms before, during, or after opioid symptoms, and 15 patients (42%) had only opioid symptoms [81]. Therefore, diphenoxylate-atropine overdoses could be considered a long-acting opioid overdose that may include manifestations of atropine toxicity. The respiratory and CNS depression can recur 12 to 24 hours after the ingestion. This could be the result of the accumulation of an active long-acting opioid metabolite.

Most patients recover after receiving only supportive care. Usually patients do not need specific treatment for their atropine toxicity but all of the severe cases require a narcotic antagonist for the treatment of diphenoxylate toxicity. In overdoses, naloxone is the treatment of choice for narcotic symptoms. Inducing vomiting with syrup of Ipecac is not recommended for asymptomatic patients because CNS and respiratory depression may develop in these patients an hour or two after ingesting lomotil tablets. Gastric lavage, if the patient presents early after his ingestion, followed by activated charcoal is the recommended treatment. Because of the likelihood of reabsorption of diphenoxylate or its metabolite from the intestine, repeated administration of activated charcoal during the course of significant intoxications is recommended. Naloxone by continuous infusion may be an alternative to oral activated charcoal when the patient has intestinal ileus or gastric atony. Signs and symptoms following an intoxication usually occur two to four hours after the ingestion. However, late opioid symptoms may occur 12 to 24 hours after the ingestion. Therefore, at least 12 hours of observation are required to detect initial symptoms. Intensive monitoring of patients with respiratory difficulty or in an unconscious state should be continued 12 to 24 hours after the

disappearance of these manifestations. Other medical complications encountered include: aspiration pneumonia, cortical blindness and three patients are reported to have deceased after they developed cerebral edema [83–89].

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10. Antiarrhythmics

Because of their actions on the heart, antiarrhythmic drugs generally have a low toxic-therapeutic index and overdoses are often life-threatening. Antiarrhythmic drugs are commonly classified by general mechanisms of action as described by Vaughn-Williams, as noted in Table 10.1. Specific drugs belonging to these classes, along with typical therapeutic doses, therapeutic concentrations and major types of toxicity in overdose are noted in Table 10.2.

Classifying drugs in this way is helpful in understanding and predicting adverse effects of overdose. Drugs within a class tend to have similar manifestations at toxic levels. This chapter will consider class I (excluding phenytoin) and class III antiarrhythmic agents. Class II agents (β-blockers) and class IV agents (calcium channel blockers) are described in Chapter 12 of this volume.

Class	Action	Typical ECG changes*
I	Depress fast response channels via action on sodium current	
IA	Decrease the maximum rate of rise of phase 0 and prolong repolarization of action potential	Minimal prolongation of QRS; prolongation of J–T (Q–T) interval
IB	Slight effect on phase 0; tends to shorten action potential duration	No effect
IC	Depression of maximal rate of phase 0 depolarization; no effect on repolarization	Prolongation of QRS interval
II	Sympathetic blockade	Slowing of heart rate; prolongation of P–R interval
III	Prolongation of action potential duration	Prolongation of J–T (Q–T) interval
IV	Blockade of slow calcium channels	Slight slowing of heart rate prolongation of P–R interval

*At therapeutic doses

Table 10.1. *Vaughn-Williams classification of antiarrhythmic drugs*

Class	Average drug	Major route of half-life (h)	Therapeutic daily elimination	Therapeutic serum dose (mg)	Major levels (mg/l)	Toxicity
IA	Quinidine	6–8	L	800–2400	2–4	H,V,B
	Procainamide	3–4	L,K	1000–4000	4–10	H,V,B
	Disopyramide	6–8	L,K	400–800	2–5	H,V,B
IB	Lidocaine	1–2	L	15–55 (mg/h/IV)	1.5–5.5	S,B,H
	Mexiletine	9–12	L	600–1200	0.8–2.0	S,B,H
	Tocainide	11–13	L,K	800–2400	3–10	S,B,H
IC	Encainide	12	L	75–300	—	B,V,H,S
	Flecainide	15	L,K	200–600	0.4–1.0	B,V,H,S
	Lorcainide	10	L	200–600	—	
	Propafenone	3–7	L	450–900	500–1000	S,H,B
	Moricizine	2–4	L	600–900	—	H,V,B
II	Beta blockers	—		—	—	B,H
III	Amiodarone[a]	50 days	L	200–600	0.5–3.0	B,V,H
	Acecainide (N-acetylprocainamide)	6	K,L	3000–4500	9–32	B,H
	Sotalol[a]	7–15	K	160–640	—	B,V,H
	Bretylium	14	K	5–10 (mg/h/IV)	—	H
IV	Calcium antagonists	—	L	—	—	B,H

a = also class II activity; L = liver; S = seizures; H = hypotension; K = kidney; B = bradyarrhythmias; V = ventricular arrhythmias.

Table 10.2. *Typical therapeutic doses, therapeutic concentrations and major types of toxicity in overdoses of antiarrhythmic drugs*

CLASS IA ANTIARRHYTHMIC DRUGS

For a recent review, see Ref. [1].

Mechanisms of toxicity

Class IA antiarrhythmic drugs decrease rapid sodium conductance through the sodium channel of the cardiac cell membrane during phase 0 depolarization and lengthen the action potential duration. Interference with the sodium current decreases the maximum rate and amplitude of the cardiac action

potential. Depression of slow inward calcium and outward potassium currents may account for the reduced action potential plateau (phase 2), and the prolonged terminal repolarization (phase 3). These drugs also reduce the rate of spontaneous depolarization (phase 4), although the mechanism remains unclear. The resultant physiologic effects are prolongation of the effective refractory period, decreased automaticity of pacemaker cells and slowing of conduction through the heart.

Quinidine, the prototypical class IA agent, produces dose-dependent changes in the electrocardiogram. With rising plasma concentrations, QRS duration widens as a result of slowing of intraventricular conduction, and Q–T interval increases as a result of delayed repolarization. Increases in the Q–T interval and, to a lesser extent, the QRS interval values are seen at therapeutic blood concentrations, although P–R intervals usually do not change. Clinical electrophysical studies show that quinidine prolongs the effective refractory period of the atrium, shortens the A–H interval (A–V nodal conduction) and prolongs the H–V interval slightly (His–Purkinje system conduction). A–V nodal conduction is mediated by opposing physiological factors, discussed below. ECG changes induced by procainamide and disopyramide are similar to those of quinidine, but less pronounced at similar therapeutic concentrations of the drugs.

During therapeutic use, several autonomic effects combine to attenuate depression of automaticity. Quinidine produces arteriolar and venous dilation by both direct action on vascular smooth muscle and β-adrenergic blockade. Procainamide causes vasodilation by inhibiting ganglionic transmission. Vasodilation elicits baroreceptor-mediated reflex sympathetic stimulation. In addition, disopyramide, and to a lesser extent quinidine and procainamide, have significant anticholinergic activity. Thus, adrenergic stimulation and cholinergic inhibition can increase sinus rate and enhance A–V nodal conduction during therapeutic use; however, in overdose situations, depressed automaticity and conduction velocity predominate, resulting in sinus bradycardia, sinus arrest, atrioventricular block, escape junctional or ventricular rhythms and asystole.

In isolated papillary muscles and in animals quinidine has direct negative inotropic effects. The ionic mechanisms are not fully understood but may include inhibition of calcium entry, either by direct inhibition or secondary to reduced intracellular sodium and consequent reduced calcium–sodium exchange, or effects of quinidine on calcium binding or release within the sarcolemma. During clinical use, however, neither quinidine nor procainamide significantly changes cardiac output or other hemodynamic parameters in most patients, probably due to opposing autonomic effects as mentioned. On the other hand, disopyramide has demonstrable negative inotropic effects during therapeutic use. The depressant effect occurs in healthy subjects but is more pronounced in patients with compromised left ventricular function.

Clinical features of toxicity

Clinical features of overdose with drugs in this class are summarized in

Table 10.3. The most serious toxicity involves the cardiovascular system, although seizures, coma and respiratory arrest may also occur. Each drug is discussed separately later in this section.

Management of intoxication

General considerations. The general management of poisoning is similar to that indicated for overdose of other drugs, as described in Chapter 1 of this volume. Specific to antiarrhythmic drugs, the induction of emesis may be dangerous since rapid loss of consciousness may occur. Decontamination procedures should be instituted even several hours after ingestion since many of these drugs have anticholinergic actions that delay absorption. All symptomatic patients should be admitted to an intensive care unit for continuous electrocardiographic monitoring. Seizures should be treated with intravenous diazepam or lorazepam, followed by phenobarbital or phenytoin.

Sodium bicarbonate and potassium. An understanding of the role of sodium lactate, sodium bicarbonate and potassium is necessary for the development of a rational approach to the treatment of poisoning by class IA and IC antiarrhythmic agents. The ability of sodium lactate to reverse cardiac manifestations of hyperkalemia, and similar ECG changes seen with hyperkalemia and quinidine intoxication, led to the proposed use of sodium lactate (rapidly metabolized to bicarbonate) to treat quinidine overdose. Since then, animal data and anecdotal reports describing dramatic clinical responses with sodium lactate have been published. Both sodium bicarbonate and sodium lactate produce rapid reversal of procainamide toxicity.

The mechanisms of the effect of hypertonic sodium lactate or sodium bicarbonate in reversing the cardiotoxicity of quinidine may be multifactorial. Possible mechanisms include: (i) increasing blood pH, (ii) increasing plasma sodium concentration, and (iii) lowering plasma potassium concentration. Acidosis decreases the rate of phase 0 depolarization of isolated Purkinje fibers, and exacerbates *in vitro* quinidine toxicity. Sodium bicarbonate reverses the toxic effects of amitriptyline (which has quinidine-like effects on the heart) to a greater degree than that achieved by increasing extracellular sodium concentration alone, indicating a direct beneficial effect of alkalinisation. An *in vivo* animal study found a significant increase in intracellular potassium and a decrease in intracellular sodium in the ventricular musculature after the administration of quinidine. By increasing extracellular sodium, hypertonic sodium bicarbonate may overcome, at least in part, the inhibition of sodium conductance. Increased extracellular sodium has been shown to reverse the electrophysiological effects of quinidine *in vitro*. The effectiveness of sodium bicarbonate may also be related in part to lowering of the extracellular potassium levels, which also enhances sodium conductance. By modulating the magnitude of the inward sodium current and rate of rise of action potential, extracellular potassium levels influence the electrophysiological effects of quinidine. *In vivo* animal experiments demonstrated that hyperkalemia aggra-

Central Nervous System	
Lethargy, confusion, coma	
Respiratory arrest	
Seizures*	
Gastrointestinal*	
Vomiting	
Abdominal pain	
Diarrhea	
Cardiovascular	
Tachyarrhythmias	
	sinus tachycardia (mild poisoning)
	ventricular tachycardia (often polymorphic)
	ventricular fibrillation
Depressed automaticity and conduction	
	QRS and Q–T interval prolongation
	bundle branch block
	sinus bradycardia
	sinoatrial block, sinus pauses and arrest
	atrioventricular block
	atrioventricular junctional or ventricular bradycardia
	asystole
Hypotension	
	vasodilation
	depressed myocardial contractility and low cardiac output
Metabolic and other features	
Hypokalemia	
Metabolic acidosis	
Cinchonism#	
Anticholinergic signs and symptoms (urinary retention, mydriasis, dry mucous membranes)+	

*Primarily quinidine; #Reported for quinidine only; +Primarily disopyramide.

Table 10.3. *Clinical features of quinidine, procainamide and disopyramide overdose*

vates quinidine toxicity, while hypokalemia reduces it. An *in vitro* study of procainamide also showed that drug-induced conduction defects were more pronounced when the extracellular potassium level was increased. Although controlled experimental data are lacking, treating serious quinidine or other class IA antiarrhythmic drug overdoses with sodium bicarbonate is rational. Repeated bolus injections of sodium bicarbonate should be given as needed to keep arterial pH between 7.45 and 7.5.

Because hypokalemia has been shown to be protective against quinidine and procainamide intoxication in experimental animals, moderate hypokalemia (3–3.5 mEq/l) in the presence of depressed myocardial conduction probably should not be treated. The clinician must recognize that the recommendations regarding hypokalemia are based on theoretical considerations.

Arrhythmias. Because of the vagolytic effects common to class IA drugs, sinus tachycardia can be seen early in overdose and generally requires no specific therapy. In the presence of symptomatic sinoatrial or atrioventricular block or other bradyarrhythmias, insertion of a cardiac pacemaker is warranted. Severely depressed automaticity and conduction caused by the class IA antiarrhythmic drugs may render the myocardium relatively refractory to electrical stimulation; as a result, higher than usual voltages may be necessary for successful intracardiac pacing, or the pacemaker may not capture at all. Isoprenaline (isoproterenol) reverses the effects of quinidine on automaticity and conduction *in vitro* and in animals and may be useful in managing quinidine-induced bradyarrhythmias.

Ventricular ectopy and ventricular arrhythmias, which are common with class IA drug intoxication, can be difficult to treat. Lidocaine (lignocaine), phenytoin, isoprenaline, bretylium and overdrive pacing have been used successfully to control quinidine-induced ventricular arrhythmias. The use of another class IA or a class IC agent (flecainide, encainide or propafenone) to treat ventricular arrhythmias induced by a class IA drug is expected to be ineffective or to aggravate the arrhythmias. Lidocaine and phenytoin exhibit electrophysiological effects that are distinct from those of quinidine: in therapeutic doses, they generally do not depress conduction or automaticity. Both may shorten the Q–T interval, and phenytoin may reduce the QRS duration as well. Isoprenaline increases the automaticity of the sinoatrial node, raises atrioventricular conduction and accelerates conduction and repolarization, thereby inhibiting the firing of junctional or ventricular pacemakers. It has been used successfully to treat recurrent ventricular flutter due to quinidine. Bretylium decreases intra-atrial and His–Purkinje conduction times *in vivo*, and has been used to treat quinidine-induced ventricular tachycardia in humans. Quinidine-induced ventricular tachycardia during therapeutic use has been successfully treated by overdrive pacing via an intracardial pacemaker.

For polymorphous ventricular tachycardia (torsade de pointes), magnesium, overdrive pacing and isoprenaline may be used. In a series of patients with polymorphous ventricular tachycardia induced by quinidine, procainamide or disopyramide, lidocaine was found to be inconsistently effective, and atrial or ventricular pacing universally effective [2]. A series of patients with drug-induced polymorphous ventricular tachycardia were successfully treated with intravenous magnesium sulfate, but magnesium was effective only in patients with Q–T interval prolongation [3]. The initial bolus dose of magnesium sulfate was 2 g, with repeat doses or continuous infusions given as needed. *In vitro* experiments suggest magnesium may abolish torsade de pointes by suppressing early after-depolarization [4].

Hypotension and shock. Hypotension may be due to decreased systemic vascular resistance and/or decreased cardiac output secondary to myocardial depression. The latter is most significant in cases of severe intoxication. Fluid resuscitation is usually effective in reversing hypotension from vasodilatation but, if blood pressure does not respond to fluids, vasoconstrictor drugs such as

norepinephrine (noradrenaline) or dopamine should be used. Hypotension has been successfully reversed with epinephrine (adrenaline) in a procainamide overdose and with dopamine in a disopyramide poisoning.

Placement of a pulmonary arterial catheter may help guide appropriate therapy by differentiating the mechanisms of hypotension. If both cardiac output and cardiac filling pressure are low, more fluids are needed. If cardiac output is low despite adequate filling pressure, inotropic agents should be used: isoprenaline was the most effective in reversing disopyramide-induced myocardial depression in animal studies. If cardiac output is adequate but vascular resistance is low, vasopressors should be given.

Severe cases of poisoning with shock due to myocardial depression may not respond to inotropic therapy. Yet if the patient can be supported for several hours until the drug is eliminated, myocardial function should return to normal. In these circumstances, extracorporeal circulatory assistance techniques may be beneficial. Intra-aortic balloon pump assistance has been used successfully in one case of quinidine overdose. Likewise, cardiopulmonary bypass, allowing time for intrinsic drug metabolism, has been used successfully for cardiogenic shock due to overdoses with tricyclic antidepressants, verapamil and propanolol, and should be considered for antiarrhythmic poisoning unresponsive to medical therapy.

Accelerated drug removal. Extracorporeal drug removal is expected to be of little benefit for most antiarrhythmic drug overdoses owing to extensive tissue distribution. Exceptions are disopyramide and procainamide, which are reasonably good candidates for hemoperfusion or hemodialysis. These procedures are discussed in more detail under the discussion of individual drugs. Acidification of the urine can significantly increase the renal clearance of many of these antiarrhythmic agents which are weak bases. However, little clinical benefit is expected because metabolism is primarily hepatic, and systemic alkalinization rather than acidification is essential for the treatment of cardiotoxic effects.

Specific drugs

Quinidine

(1) *Ventricular tachyarrhythmias.* The toxicity of quinidine (as well as other type IA and IC antiarrhythmic drugs) of greatest concern is its proarrhythmic effect. Ventricular tachycardia, often of the torsade de pointes type, leading to syncope or sudden death, has been recognized for many years, known as "quinidine syncope". Similar proarrhythmic effects are seen with other type IA as well as type IC and occasionally type III antiarrhythmic drugs. While massive overdose with quinidine does not usually present with torsade de pointes, this arrhythmia is always a concern in intoxicated patients and will therefore be discussed in some detail.

The typical polymorphous ventricular tachycardia produced by antiarrhythmic drugs is characterized by progressive changes in amplitude and polarity of

the QRS complex, and Q–T interval prolongation. However, drug induced ventricular tachycardia is often not of the classic torsade de pointes type and the QRS complex may not show the characteristic twisting and the Q–T interval may not be prolonged. The mechanism of polymorphous ventricular tachycardia due to antiarrhythmic drugs is not fully understood, but there is evidence that it involves early after-depolarizations [5]. Early after-depolarizations are secondary depolarizations that occur before repolarization is complete, usually occurring at the end of the T wave on the surface ECG. The magnitude of the after-depolarization is greater with a longer preceding R–R interval. Therefore, a sinus pause often precedes the onset of polymorphous ventricular tachycardia.

The most consistent clinical finding during syncopal episodes is ECG evidence of delayed repolarization, manifested by a prolonged Q–T interval and/or the presence of a large U wave. Generally, the QRS interval is within normal limits. There is no correlation between blood concentrations of quinidine or its metabolites and the risk of syncopal episodes: in one recent series, 12 of 14 syncopal patients had quinidine concentrations below or within the therapeutic range [6]. Generally, syncopal episodes occur early in treatment, within the first few days, although they may occur after months of uneventful therapy.

"Idiosyncratic" reactions to quinidine may be to some degree predictable. In one review, 91% of those who had syncopal episodes were receiving quinidine to terminate atrial fibrillation or flutter or to prevent recurrence of the two arrhythmias [7]. Of the same group, 89% were taking digoxin concurrently or had very recently discontinued digoxin therapy. Hypokalemia may be contributory: in one series, two thirds of patients with syncope had serum potassium levels of less than 4 mEq/l [8]. A review of patients with ventricular fibrillation during antiarrhythmic therapy found left ventricular ejection fractions to be significantly lower in patients who had arrhythmias than in those who did not [9], and similar findings were noted in patients who had aggravation of ventricular arrhythmias during antiarrhythmic therapy [10]. Those with ejection fractions of less than 35% were 2.2 times more likely to experience worsening of arrhythmias, and those with underlying sustained ventricular tachycardia or ventricular fibrillation were 3.4 times more likely to do so. Another predictor of quinidine syncope is the presence of Q–T interval prolongation prior to initiation or after the cessation of quinidine therapy.

The ventricular tachycardia that is seen in severe quinidine overdose is presumably due to reentry owing to localized areas of depressed conduction with unidirectional block. As widening of the QRS complex is commonly seen with quinidine overdose, a wide complex may also be observed with sinus or other supraventricular rhythm. Serial electrocardiograms may be useful in distinguishing a supraventricular rhythm with wide QRS from ventricular tachycardia.

(2) *Depression of automaticity and intracardiac conduction.* Unlike quinidine syncope, depression of myocardial function is clearly a dose-related effect. Evidence of slowing of conduction is seen at therapeutic doses, with

prolongation of the Q–T interval the earliest and most consistent finding. Increase in the width of the QRS complex of more than 25% over baseline has been used as an indication of toxicity; more severe toxicity results in further widening with abnormal morphology of the QRS complex, bundle branch block and sinoatrial and/or atrioventricular block. Arrhythmias indicative of depressed automaticity and conduction include sinus bradycardia, sinus pause or arrest, junctional or ventricular escape rhythms, varying degrees of atrioventricular block and asystole. Underlying sinus node dysfunction may be uncovered by quinidine and result in sinoatrial block. Early toxicity may present as sinus or atrial tachycardia due to vagolytic and reflex adrenergic effects. However, in severe overdose, depressed automaticity dominates.

(3) *Hypotension and shock.* Hypotension occurs frequently after intravenous quinidine use, particularly with rapid infusion. At low doses, it is due to direct vasodilatory effects of the drug. With severe overdoses, circulatory collapse is common and is due to myocardial depression. The clinical course of severe quinidine overdose is characterized by profound shock, recurrent arrhythmias, central nervous system depression or seizures, and oliguria. Resolution of symptoms may require 48 hours or longer. Pulmonary edema, a consequence of depressed myocardial contractility with subsequent acute left ventricular failure, may be seen after quinidine overdose.

(4) *Accelerated drug removal.* Quinidine is widely distributed to body tissues, with an apparent volume of distribution (Vd) estimated at 3 l/kg. It is substantially (70–90%) bound to plasma proteins. Quinidine is metabolized primarily by hydroxylation in the liver. Some of its metabolites (3-hydroxy-quinidine, 2′-oxoquinidione and quinidine-N-oxide, as well as a manufacturing contaminant, dihydroquinidine) are pharmacologically active [11]. 3-hydroxy-quinidine, a major metabolite, is about 20% as active as quinidine and has similar effects. About 20% of quinidine is eliminated unchanged in the urine, but urinary excretion has been reported to be increased in acidic urine. The average half-life of quinidine at therapeutic doses is 6–8 hours, with large intersubject variability.

Extracorporeal removal of quinidine has been attempted for severe intoxication. As would be predicted from the pharmacokinetic parameters of the drug, hemodialysis does not significantly decrease the total body burden of quinidine. The contribution of peritoneal dialysis in removing quinidine during long term quinidine therapy is negligible.

Procainamide

(1) *The cardiovascular effects of procainamide* are similar to those of quinidine. Procainamide can induce ventricular tachyarrhythmias including torsades de pointe after intravenous or oral therapy. However, the proarrhythmic risk of procainamide appears to be less than that of quinidine or disopyramide. Hypotension occurs mainly with intravenous use, especially if the rate of infusion exceeds 20 mg/min. Occasionally, hypotension has been reported after oral dosing. Acute procainamide overdose results in severe hypotension and

life-threatening arrhythmias. Severe procainamide intoxication may result in the inability to electrically pace the heart due to high pacing thresholds with failure to capture.

(2) *Acecainide* (N-acetyl-procainamide, NAPA) is a major metabolite of procainamide, and is pharmacologically active as an antiarrhythmic agent. The electrophysiological effects of acecainide are consistent with the actions of a class III antiarrhythmic drug [12]. At therapeutic concentrations, acecainide does not increase P–R or QRS intervals but does increase the Q–T interval to the same degree as its parent compound. In animals acecainide exerts positive inotropic effects but has negative chronotropic and hypotensive activity similar to that of procainamide. In a study of patients with arrhythmias, acecainide produced weak peripheral arterial and venous dilatory effects which elicited a reflex increase in heart rate, resulting in little change in cardiac output [12]. Acecainide can cause cardiac toxicity which may be seen with or without concurrent high concentrations of procainamide and, given alone, it has produced torsades de pointe [2,13]. Accumulation of acecainide during procainamide therapy occurs mainly in the presence of decreased renal function. Hypotension, progressive widening of QRS and Q–T intervals, torsades de pointe and severe left ventricular depression were described in four patients with toxic acecainide concentrations [14].

(3) *Accelerated drug removal.* Procainamide is extensively distributed to body tissues. The Vd is estimated at 2 l/kg, but may decrease with cardiac failure or shock. Procainamide is only slightly bound to plasma proteins, averaging 15–25%. Acecainide has a smaller volume of distribution (1.5 l/kg) and is less protein bound (10%) than procainamide. Approximately 50% of procainamide is excreted unchanged in the urine. Glomerular filtration and active tubular secretion are the most important mechanisms of renal excretion; excretion is independent of urinary pH. Procainamide is also metabolized by the liver, where it is primarily acetylated to acecainide. Steady-state acecainide concentrations are generally 2–3 times greater than those of the parent compound. The generation of acecainide is faster and more extensive in genetically fast acetylators. About 60–90% of an orally administered dose of acecainide is excreted unchanged renally.

The half-life of procainamide averages 3 hours in healthy subjects, but may be prolonged to 16 hours with renal failure. The half-life of acecainide averages 6 hours in healthy subjects but increases predictably in the presence of renal dysfunction, and may be prolonged to 42 hours in functionally anephric patients. Continuous ambulatory peritoneal dialysis contributes little to the clearance of procainamide or acecainide. In overdoses, half-lives of 8.8 and 10.5 hours for procainamide and 36 hours for acecainide have been reported.

Enhancement of excretion has been attempted following procainamide overdose. Peritoneal dialysis has proved ineffective. Hemodialysis doubles the clearance of procainamide and increased that of acecainide 4-fold. A 4-hour hemodialysis decreased the acecainide concentration from 43–20 mg/l with resolution of cardiotoxicity, but the procainamide concentration was virtually

unchanged [15]. Hemodialysis, charcoal hemoperfusion and combined hemodialysis-hemoperfusion were performed in a patient with severe procainamide toxicity: clearances of procainamide and acecainide were higher during hemoperfusion than during hemodialysis, and the combined processes removed acecainide 3 times more effectively than hemodialysis alone [16]. Continuous arteriovenous hemofiltration has been used with and without hemodialysis in 2 patients with underlying renal failure [17]: clearances were not calculated, but estimated half-lives for acecainide were 1.5 days for hemodiafiltration and 3.1 days for hemofiltration, compared with 4–7 days for hemodialysis. Resin hemoperfusion was used in a patient with suspected acecainide toxicity with a markedly elevated acecainide concentration, and this procedure increased the blood clearance to 7.3 l/h compared with 1.2–3.2 l/h during hemodialysis [18]. Resin hemoperfusion has effectively reversed acecainide-induced ventricular arrhythmias, and dramatically decreased acecainide concentrations, in other patients as well.

Disopyramide

(1) *Cardiovascular effects.* At therapeutic doses, changes in QRS interval and Q–T duration are minimal. However, "disopyramide syncope" (runs of paroxysmal ventricular tachycardia or fibrillation with sudden loss of consciousness) has been described. As with quinidine, the episodes occur unexpectedly and at therapeutic doses. Generally, the malignant arrhythmias occurred within one month of initiation of disopyramide therapy. Electrocardiograms preceding or following syncopal episodes showed markedly prolonged Q–T intervals, often with prominent U waves, but no QRS widening. With elevated serum concentrations of disopyramide, the QRS interval is markedly widened and its configuration often bizarre.

Of the three class IA agents, disopyramide has the most pronounced negative inotropic effects. While negative inotropic effects do occur in healthy people, they are more pronounced in patients with pre-existing left ventricular dysfunction. Disopyramide induces or exacerbates congestive heart failure in 50% of patients with underlying left ventricular dysfunction, while the incidence averages 5% in those without heart failure. Disopyramide therapy has induced cardiogenic shock in patients with heart failure. Cardiovascular collapse and death during disopyramide therapy has been described in patients with severe left ventricular failure: ECG changes prior to collapse include lengthening of the QRS and Q–T intervals, sinus bradycardia and atrioventricular block.

Overdoses of disopyramide can cause cardiovascular collapse unresponsive to standard therapy. In dogs poisoned with the drug, circulatory collapse resulting in a sudden drop in blood pressure and cardiac output may occur without obvious premonitory changes in the ECG. Respiratory arrest then follows. Reports of disopyramide overdose in humans are characterized by early loss of consciousness, respiratory arrest, tachy- or bradyarrhythmias and cardiac arrest. Despite initial response to resuscitation and antiarrhythmic

therapy, patients may subsequently develop malignant arrhythmias and death. Pulmonary edema is an almost universal finding at necropsy, presumably secondary to compromised cardiac function. A case series of 106 acute disopyramide poisonings reported early development of cardiovascular disorders including shock, cardiac arrest, atrioventricular block, intraventricular block and malignant arrhythmias [19]. The mortality rate was 12.2%. In this series, the acute toxic dose in otherwise healthy adults was estimated to be 1.5 g.

Two cases of apparent cardiovascular toxicity due to disopyramide, associated with QT prolongation and episodes of polymorphic ventricular tachycardia, have been reported in elderly patients formerly on a stable dose of disopyramide after initiation of erythromycin therapy [20].

(2) *Accelerated drug removal.* The Vd of disopyramide is small (0.8 l/kg). Plasma protein binding of disopyramide is concentration-dependent, decreasing as the concentration rises. At concentrations above the therapeutic range, the percentage of bound drug is less than 30%. On average, 55% of disopyramide is excreted unchanged in the urine, and renal excretion is independent of urinary pH. 20% of a dose is excreted as monodealkylated disopyramide, which is weakly active, and 10% as other metabolites.

The plasma half-life of disopyramide in healthy adults is approximately 6–8 hours. Renal clearance is markedly reduced in the presence of severe renal dysfunction (creatinine clearance <8 ml/min), and the half-life of disopyramide in such patients ranges from 14–43 hours.

The relatively small Vd, low protein binding at toxic concentrations and low intrinsic clearance make disopyramide a good candidate for extracorporeal removal. In patients on long-term hemodialysis the half-life of disopyramide is decreased by 45–72% during hemodialysis. Hemoperfusion with columns containing either uncoated charcoal or "Amberlite XAD-2" resin are effective in reversing clinical signs of toxicity in dogs, and resin hemoperfusion has been used successfully to reduce blood concentrations and toxic effects in disopyramide poisoned patients.

Hemofiltration has been reported to be of benefit in the treatment of cardiogenic shock and uric renal failure due to disopyramide intoxication. The clearance of disopyramide was estimated to be 30 ml/min [21]. The procedure, used on two occasions in this patient, removed 117 and 86 mg of the drug respectively, not a very large amount of the total body burden.

CLASS IB ANTIARRHYTHMIC DRUGS

For a recent review, see Ref. [22].

General considerations

Within this group are lidocaine, widely used as a local anesthetic and the parenterally administered antiarrhythmic group drugs, mexiletine and to-

cainide, structural analogs of lidocaine. Mexiletine and tocainide have actions similar to those of lidocaine, but have higher oral bioavailability and hence are useful as oral antiarrhythmic agents. Most of the adverse effects reported with these agents are dose-related.

Intoxication with lidocaine is relatively common. Ten to twenty-five per cent of the adverse reactions are potentially life threatening. Such intoxications can occur as acute massive overdoses, such as after inadvertent acceleration of maintenance intravenous infusions or with accidental injection of doses meant for dilution (20% solutions) rather than those intended for direct administration (2% solutions) [23]. Acute injection of lidocaine has been reported as a method of homicide [24]. More commonly, intoxications result from rapid injections of therapeutic doses of lidocaine in patients with circulatory insufficiency, during maintenance infusions, particularly when clearance is abnormally low due to heart failure, liver disease, advanced age and/or interactions with drugs that slow the metabolism of lidocaine; or after use of excessive doses or with inadvertent intravenous administration during local anesthesia, including epidural and paracervical blocks. Occasionally, poisoning occurs with inadvertent intramuscular injection during local anesthesia or after swallowing viscous lidocaine prescribed for sore throat, the latter primarily in children [25]. Lidocaine poisoning has also resulted from application of a cream containing lidocaine to a large area of diseased skin [26]. Lidocaine has been one of the most frequently implicated drugs in causing seizures in a general medical service.

Intoxications with mexiletine and tocainide are uncommon. However, fatal overdoses have been reported. Between 30 and 50% of patients on tocainide or mexiletine suffer adverse effects, with discontinuation of therapy being required in 10–20% of cases.

Mechanisms of toxicity

Lidocaine and other type IB agents act primarily to inhibit sodium movement across cell membranes. In peripheral nerves this action results in a decreased rate and degree of depolarization of nerve cells, failure to achieve the threshold potential necessary to propagate action potentials, and hence results in conduction blockade and anesthesia. In the heart, lidocaine also inhibits sodium conductance, decreasing the maximal rate of depolarization of myocardial conducting cells. This effect is more prominent in cells that are ischemic and at rapid heart rates. For this reason lidocaine is most effective in the termination of rapid ventricular tachycardia, especially during acute ischemia or after myocardial infarction. Lidocaine may also increase the ventricular fibrillation threshold. At therapeutic doses lidocaine has minimal electrophysiological effects on normal cells.

At therapeutic concentrations type IB drugs do not affect the QRS interval and either have no effect or slightly shorten the QT (J–T) interval on the surface electrocardiogram. They have minimal depressant action on the myocardium and are well tolerated by most patients with myocardial disease. The

major difference among the three type IB drugs is their pharmacokinetic properties. Most of the published experience with the toxicology of these agents is with lidocaine. The effects of mexiletine and tocainide appear to resemble those of lidocaine. In excessive doses lidocaine can inhibit the sodium channel even in normal tissues. The result may be a clinical picture similar to that seen in quinidine poisoning: marked slowing of cardiac conduction with development of a wide QRS complex on the ECG and progressive heart block; depressed automaticity, resulting ultimately in a slow ventricular rhythm or asystole; and vasodilation.

Central nervous system toxicity, particularly seizures and respiratory arrest, presumably results from disturbances in ion transport across brain cell membranes. Inhibitory neurons are blocked first, producing excitatory stimulation and convulsions, while at higher concentrations both inhibitory and excitatory neurons are inhibited, resulting in generalized central nervous system depression.

Clinical features of toxicity

Clinical features of overdose with drugs in this class are summarized in Table 10.4.

Central Nervous System	
Lightheadedness, visual disturbance	
Paresthesias, dysarthria, ataxia, memory loss	
Euphoria, agitation, drowsiness	
Confusion, disorientation, psychosis, coma	
Shivering, muscle twitching, tremor	
Hypotonia (neonates)	
Seizures	
Respiratory arrest	
Cardiovascular	
Arrhythmias	
	sinus arrest, sinus bradycardia
	atrioventricular junctional or ventricular bradycardia
	second and third degree heart block, asystole
	QRS interval prolongation*
	ventricular tachycardia or fibrillation#
Hypotension	
	vasodilation
	depressed myocardial contractility and low cardiac output
Gastrointestinal	
Nausea, vomiting	

*Massive poisoning; #Proarrhythmic effects of mexiletine and tocainide; may occur at therapeutic doses.

Table 10.4. *Clinical features of lidocaine, mexiletine and tocainide intoxication*

Central nervous system (CNS). The most common toxicity of lidocaine and related drugs involves the CNS. CNS symptoms almost always precede serious cardiovascular poisoning except with massive intravenous overdoses. Even with therapeutic doses of lidocaine patients may describe dizziness, drowsiness, paresthesias or euphoria. Typically, with progressive levels of intoxication, lidocaine produces lightheadedness or dizziness, visual disturbances such as difficulty focusing, paresthesias, tinnitus, drowsiness, confusion, agitation and/or disorientation and even hallucinations and psychosis.

Signs of CNS toxicity include shivering, muscle twitching, ataxia, dysarthria, nystagmus and tremors. With massive overdoses, seizures, coma and respiratory arrest may occur. If intoxication develops gradually such as when lidocaine is absorbed from subcutaneous or intramuscular sites or during a constant intravenous infusion, a progression of symptoms and signs is often observed. However, with rapid administration of lidocaine or in the presence of other CNS-depressant drugs, seizures and/or coma may be the first sign of intoxication. Lidocaine intoxication in the newborn, occurring as a result of inadvertent injection into the fetal scalp or cranium during local anesthesia (caudal or paracervical block or episiotomy), produces apnea, bradycardia, hypotonia and seizures. Dilated pupils and loss of the oculocephalic reflex may be observed. Animal experiments show the seizure threshold to be markedly reduced when lidocaine is given to dogs chronically dosed with tocainide. This potentially dangerous situation could occur when lidocaine is used as a local anesthetic in patients on other oral class IB agents.

CNS side effects are common with mexiletine and tocainide even at therapeutic doses. Such side effects require termination of therapy in a significant number of patients. Seizures have been observed with overdoses of both drugs.

Cardiovascular toxicity. The effects of lidocaine on the cardiovascular system are biphasic. With mild intoxication, blood pressure, heart rate and cardiac output may be initially elevated due to catecholamine release and peripheral vasoconstriction. At higher doses, heart rate, conduction velocity and contraction of the heart may be depressed and blood vessels become dilated. This may result in arrhythmias, shock or circulatory collapse. Similar findings have been reported in overdoses of both mexiletine and tocainide. Arrhythmias include sinus bradycardia, sinus arrest, AV nodal or ventricular rhythms, second and third degree heart block and asystole [27]. Other ECG changes after massive overdose include prolongation of the PR and QRS intervals. QRS complex widening has been reported after rapid intravenous injection, and in one case during oral therapy with tocainide in patients following acute myocardial infarction [28,29]. Large doses, such as 1–2 g of lidocaine intravenously, can result in immediate asystole, apnea and convulsions.

Arrhythmias may also occur at therapeutic doses. In patients with underlying sick sinus syndrome or conduction disease, sinus arrest, marked bradycardia and AV block have been reported. Asystole has been reported in patients with conduction abnormalities who were given metoprolol followed by intravenous tocainide. A combined overdose with mexiletine, nifedipine and nitro-

glycerine in a 50-year-old man resulted in variable second and third degree AV block, with periodic bradycardia as low as 40 per minute, as well as seizures and hypotension [27]. It is unclear how much the mexiletine vs. the nifedipine contributed to these arrhythmias. Lidocaine may increase ventricular ectopy, particularly in the early stages immediately following acute myocardial infarction. Proarrhythmic actions of mexiletine and tocainide, including ventricular tachycardia (sometimes torsade de pointes) or ventricular fibrillation occur in 5–10% of treated patients. This incidence is less than that reported with class IA and IC agents.

Management of intoxication

General management is similar to that described for other drug overdoses and in the section on IA antiarrhythmic drugs. Intravenous lidocaine should of course be discontinued immediately.

Central nervous system toxicity. Seizures should be treated with intravenous diazepam or lorazepam initially and then, if necessary, phenobarbitone. Most lidocaine-induced seizures are brief in duration, but in massive poisoning status epilepticus may ensue. In status epilepticus refractory to anticonvulsive medications barbiturate, anesthesia with continuous EEG monitoring should be considered.

Arrhythmias. Bradyarrhythmias producing hypotension may be temporarily managed by infusion of isoprenaline (isoproterenol). However, insertion of a temporary pacemaker is the treatment of choice. Asystole due to a massive accidental overdose of lidocaine during coronary artery bypass graft surgery was treated successfully with combined atrial pacing and infusion of isoprenaline, allowing discontinuation of cardiopulmonary bypass [30]. Theoretically, based on its efficacy in treating arrhythmias due to drugs with quinidine-like activity, hypertonic sodium bicarbonate should be of benefit in massive intoxications with prolongation of the QRS interval on ECG.

Hypotension. Hypotension may be due to decreased cardiac output (owing to arrhythmias or myocardial depression), or to decreased systemic vascular resistance. Hypotension should be treated with fluids, and if necessary, vasoconstrictor drugs such as noradrenaline (norepinephrine) or dopamine. Isoprenaline or other inotropic drugs may be useful in the presence of depressed myocardial contractility. Extracorporeal circulatory assistance may provide short term support for the severely intoxicated patient, allowing time for lidocaine to be distributed to the peripheral tissues, and as a means to maintain liver circulation and allow lidocaine to be metabolized. This has been evaluated in experimental animals and been used to manage two patients who were accidentally overdosed by injection of a 20% lidocaine solution [30,31].

Accelerated drug removal. Repeated dose charcoal has not been evaluated for treatment of intoxication of any of the drugs in this class. In theory it should be of some benefit for treatment of intoxication with tocainide, which as a relatively small volume of distribution and low intrinsic clearance, and is not

highly protein-bound. Acidification of the urine will increase the renal clearance of all drugs in this class. However, it is unlikely to be of clinical significance, except possibly for tocainide which is excreted to a considerable extent in the kidney and has a relatively low intrinsic clearance. In considering acidification therapy, the risks of aggravating acidemia and the associated aggravation of adverse renal effects due to myoglobinuria (if present) in convulsing patients need to be weighed against the benefits of accelerated renal clearance.

Because lidocaine has a moderate volume of distribution, hemoperfusion is potentially beneficial, particularly when metabolic clearance is reduced due to circulatory collapse or severe liver disease. Hemodialysis is expected to be of less benefit due to the degree of protein binding.

Tocainide is significantly removed by hemodialysis and similarly should be effectively removed by hemoperfusion. Since the intrinsic clearance of tocainide is low (200 ml/min, or less than in the presence of renal insufficiency), adding a hemoperfusion or hemodialysis clearance of 200–300 ml/min should substantially accelerate removal. However, because of the large volume of distribution these procedures need to be continued for at least several hours. In a case report, hemodialysis (4 hours) was administered to a 69 year-old man who ingested 8.4 g of tocainide [32]. The concentration fell from 34 mg/l to 23 mg/l after 2 hours of dialysis and was 2.8 mg/l the next day.

Mexiletine is rapidly metabolized, highly protein bound and extensively distributed to tissues. Therefore, it is unlikely that any extracorporeal drug removal procedure will be of use in managing intoxications with this drug.

CLASS IC ANTIARRHYTHMIC DRUGS

General considerations

The type IC antiarrhythmic drugs are in general highly effective in suppressing ventricular ectopy, and are also used to treat recurrent supraventricular tachycardias. However, in view of the increased mortality, presumably due to proarrhythmia, in patients after myocardial infarction, these agents are not widely prescribed. Nonetheless, overdoses do occasionally occur and are often life threatening.

Mechanisms of toxicity

Class IC drugs block the fast inward sodium channel, and markedly depress the maximal rate of phase zero depolarization (V_{max}), resulting in slowing of conduction. In canine cardiac Purkinje fibers the effects of flecainide to depress V_{max} are antagonized by increasing extracellular sodium concentration, suggesting that sodium may compete with flecainide for binding to the sodium channel [33]. Dissociation of flecainide from the sodium channel appears to be

very slow compared to that of quinidine or lidocaine. This may explain the marked depression of V_{max} even at low ventricular rates, as compared to quinidine or lidocaine where effects are more prominent at higher heart rates. The QRS interval is prolonged to a greater extent than that observed with type IA agents, so that changes may occur even in therapeutic doses. As described for type IA agents, the type IC drugs impair automaticity, produce conduction blocks, induce ventricular arrhythmias (both torsade de pointes and reentry types), and depressed cardiac contractility. The type IC drugs in general do not prolong ventricular depolarization or the effective refractory period, and therefore do not prolong the J–T interval. The apparent prolongation of the Q–T interval on the electrocardiogram is due primarily to QRS prolongation. The fact that these drugs slow conduction but do not prolong the refractory period may explain the propensity toward producing reentry ventricular arrhythmias [34].

Propafenone, in addition to having type IC activity, has weak β- and calcium channel blocking activity. These effects are not common at therapeutic doses, but could be relevant in overdose situations. Moricizine has electrophysiologic effects similar to flecainide, but less of a depressant effect on myocardial contractility.

Clinical features of toxicity

Flecainide administration, even at therapeutic doses, may prolong the AH, HV, PR and QRS intervals. Flecainide reduces cardiac output and increases left ventricular filling pressures, particularly in the presence of pre-existing impaired ventricular function [35]. In many such cases, flecainide precipitates or aggravates congestive heart failure. Flecainide depresses sinus node activity in patients with sick sinus syndrome and aggravates pre-existing AV nodal conduction disturbances. Proarrhythmia is a particular concern with flecainide, occurring in as many of 20% of patients with underlying cardiac disease. Usually, the arrhythmia is monomorphic and is not associated with Q–T interval prolongation, and is less likely to self-terminate than is torsade de pointes.

Intoxication with flecainide has been associated with QRS prolongation, AV block, bradycardia, ventricular tachycardia and hypotension [36–39]. Asystole may ensue. Generalized seizures have also been reported after flecainide overdose [40]. Encainide overdose in adults has produced QRS prolongation, ventricular tachycardia, bradycardia, seizures and coma [41,42]. Intoxication in a 6-month-old infant who took a single 25 mg table of encainide resulted in pallor, diaphoresis, cyanosis and shock [43]. A wide complex sinus tachycardia, followed by ventricular tachycardia and ventricular fibrillation was noted.

Propafenone overdose has been reported in a 2-year-old who ingested 1800 mg (133 mg/kg) [44]. The child experienced generalized seizures, hypotension, PR, QRS and Q–T interval prolongation, followed by bradycardia (probably an idioventricular rhythm), and then cardiac arrest.

Moricizine has proarrhythmic effects similar to those of other type IC agents. The drug is tolerated much better than flecainide or encainide in patients with impaired ventricular function. Little has been published on intoxication with moricizine.

Management of intoxication

The principles of management are similar to those described previously for the class IA antiarrhythmic drugs. As noted above, there is experimental evidence that increasing extracellular sodium concentration can ameliorate the effects of flecainide on the sodium channel [33]. Likewise, *in vivo* studies in rats have shown that hypertonic sodium bicarbonate reduces QRS prolongation induced by flecainide intoxication [45]. Either sodium bicarbonate or sodium chloride loading normalized the QRS prolongation due to O-desalkyl encainide, the active metabolite of encainide in dogs [46]. In humans, sodium lactate (250–500 mEq over 30–60 minutes) or hypertonic sodium bicarbonate (1 M) have improved hypotension and QRS prolongation in patients overdosed with flecainide or encainide [36,43]. Hypertonic sodium chloride (3 M) appeared to be useful in the treatment of refractory ventricular tachycardia, secondary to therapeutic use of encainide [42].

Accelerated drug removal interventions are not likely to be of use for type IC antiarrhythmic agents due to their extensive tissue binding with resulting large volumes of distribution. In one 55-year-old woman on chronic hemodialysis, a 3 hour charcoal hemoperfusion was performed for flecainide toxicity manifested by QRS widening and shock [47]. In 3 hours, 22.5 mg of flecainide, an insignificant amount, was removed, supporting the lack of utility of hemoperfusion. Hemodialysis may be of possible benefit for flecainide toxicity in patients with renal failure, but prolonged and repeated dialysis would be necessary.

CLASS III ANTIARRHYTHMIC DRUGS

General considerations

Class III antiarrhythmic drugs share an effect to prolong the action potential duration and the refractory period, acting at least in part through blockade of potassium channels. The most widely used of the type III agents are amiodarone, bretylium (parenteral use only) and sotalol (a beta blocker with type III antiarrhythmic activity). Acecainide (N-acetyl-procainamide) also has type III antiarrhythmic activity as mentioned earlier. This section will focus primarily on amiodarone, as adverse effects of bretylium are seen only with therapeutic dosing and sotalol is discussed in the section on beta blockers.

Mechanisms of toxicity

The pharmacology of amiodarone is complex. Its main pharmacologic action, which defines its place as a class III antiarrhythmic drug, is prolongation of action potential duration and the effective refractory period, thereby increasing the time for repolarization. Other prominent effects are depression of sinus node and AV node automaticity, slowing of AV nodal conduction and systemic vascular and coronary vasodilation. There is relatively little depression of myocardial contractility.

The underlying cellular mechanisms for these actions include blockade of the delayed outward potassium current, blockade of the inward sodium current (predominantly when the sodium channel is inactivated, that is, phases 2 and 3 of the action potential), noncompetitive β- and α-adrenergic blockade, and weak calcium channel blockade.

Clinical manifestations of toxicity

Most of the experience with amiodarone toxicity derives from chronic therapeutic dosing, with only a few reports of overdose. The main toxic concerns with chronic dosing are non-cardiac, including pneumonitis, hepatitis, hypo- and hyperthyroidism, photosensitivity, tremor and peripheral neuropathy, and corneal deposits. The reader is referred elsewhere for a detailed discussion of these toxicities [48,49].

The cardiac effects of amiodarone in therapeutic dosing include sinus rate slowing, first degree AV block or slowing of the ventricular response rate in atrial fibrillation, and Q–T (J–T) interval prolongation. A notched T wave or an abnormal wave at the end of the T wave is commonly seen. The extent of Q–T interval prolongation has been correlated with myocardial concentrations of amiodarone. Manifestations of cardiac toxicity include sinus bradycardia, high-degree AV block and proarrhythmias. Sinus node arrest has been reported, particularly in patients also receiving digoxin. The most common proarrhythmia is polymorphic ventricular tachycardia of the torsade de pointes type, believed to be related to triggered automaticity (i.e. spontaneous after-depolarizations), as discussed for quinidine earlier. The risk of polymorphic ventricular tachycardia may be increased by co-administration of type I antiarrhythmic agents. Less commonly, amiodarone may produce monomorphic ventricular tachycardia, presumably via a reentry mechanism. Aggravation of congestive heart failure has been reported, but it is unclear how much of this aggravation is drug related vs. deterioration of severe underlying myocardial disease. In general, amiodarone is tolerated well, even in patients with prior myocardial dysfunction.

A few cases of amiodarone overdose have been reported [50,51]. These patients have done well, with only mild toxicity. Toxicity has included sinus bradycardia, Q–T interval prolongation, and in one case, brief, self-limited episodes of ventricular tachycardia. Clinical manifestations of overdose may not appear for several hours after ingestion, and may last for several days.

An understanding of the pharmacokinetics of amiodarone helps clarify the common features and time course of the overdose. Amiodarone is unique among antiarrhythmic drugs as being extensively tissue bound with an enormously large volume of distribution (10–70 l/kg), which in combination with relatively slow metabolic clearance, results in a very long half-life (20–50 days). Consistent with a long half-life, it takes weeks to months of chronic daily dosing with amiodarone to achieve steady state; and this is the basis for the current practice to provide loading doses in the first few weeks. A single, even substantial overdose of amiodarone in a person not previously taking the drug is equivalent to a loading dose, and often does not result in toxic levels or toxic effects. To illustrate the point one can consider the typical pharmacokinetics of amiodarone and the total body content of amiodarone in a person taking 200 mg per day, a low dose. Assuming an oral bioavailability of 35% and an elimination half-life of 50 days, there will be about 5 g of amiodarone in the body at steady state. Thus, an overdose of twenty five 200 mg tablets would be equivalent to loading a person in anticipation of low dose maintenance amiodarone treatment.

Management of overdose

As for other antiarrhythmic intoxicated patients, patients with amiodarone overdoses should be observed with continuous cardiac monitoring for at least 1–2 days. It should be noted that amiodarone is slowly and variably absorbed from the gastrointestinal tract. Thus, maximal blood levels may not be seen for 10 hours or more after ingestion. For this reason, gastric lavage is indicated even many hours after ingestion, and patients with amiodarone overdose should be observed carefully for at least a day to assess the potential maximum absorption and toxicity.

Amiodarone is concentrated in the bile, and there is evidence of enterohepatic recycling. Oral cholestyramine has been shown to reduce the absorption and to shorten the elimination half-life of amiodarone [52]. Presumably, oral charcoal would do the same. Therefore, the use of repeated doses of oral charcoal or cholestyramine is recommended.

The definitive management of amiodarone-induced bradyarrhythmias is cardiac pacing. Isoproterenol may be used to maintain heart rate and blood pressure until a pacemaker can be inserted. Ventricular tachycardia of the torsade de pointes type can be managed with magnesium and/or overdrive pacing. Monomorphic ventricular tachycardia may be responsive to lidocaine or propanolol.

Interventions to accelerate amiodarone removal, other than repeated doses of oral charcoal or cholestyramine, are not likely to be useful. Amiodarone is extensively protein bound (98%) so hemodialysis is not of use. Hemoperfusion would be expected to remove amiodarone from the blood, but due to extensive distribution in tissues, would not be very efficacious in removing amiodarone from the body and therefore treating intoxication. Theoretically, early hemoperfusion, before tissue distribution occurred, could reduce the amount of amiodarone reaching body tissues.

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11. Digitalis

Despite the advent of newer inotropic and antiarrhythmic agents, digitalis is still one of the most frequently prescribed cardiac medications for the therapy of congestive failure or supraventricular dysrhythmias [1]. However even Withering, the English physician credited with discovering its clinical utility in 1785, recognized the classic signs of digitalis poisoning when he wrote: "*The Foxglove when given in very large doses and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death.*" [2].

Poisoning takes place in the context of one-time accidental ingestions in young children or intentional overdoses among adolescents or adults. Intoxications also occur during loading with the medication or as a result of mistakes in the calculation of a loading or maintenance dose. Chronic toxic effects are manifest among vulnerable populations (for example, patients who require a high dose and are taking concurrently potassium-wasting diuretics or those with some degree of renal insufficiency) or in the context of drug interactions which potentiate the pharmacologic activity of digitalis. Studies done in the 1970s confirmed that among hospitalized patients receiving digitalis, up to 29% experienced adverse effects associated with the drug [3–5]. Bismuth et al. [6] reported a mortality rate of 13.7% among 124 patients with digitoxin poisoning admitted to the intensive care unit in France during the late 1960s/early 1970s. Hess et al. [7] cited a mortality rate as high as 25% with massive overdoses of digitalis when only supportive care was available.

The toxicity of digitalis has undoubtedly declined since then due to several compelling reasons: (i) with a more clearly defined role for digitalis in the management of congestive heart failure and arrhythmias, supplemented by other effective cardiovascular agents, therapeutic changes allow for a lower effective digoxin dose; (ii) careful patient selection allows for the avoidance of digitalis in those patients at higher risk for toxicity; (iii) a specific radioimmunoassay has allowed accurate monitoring of the serum digoxin concentration; (iv) the manufacture of digitalis has become more standardized with the consequent improved, more consistent bioavailability of the drug; (v) increased

physician awareness of the dangers of hypokalemia in patients on long-term maintenance digitalis and its avoidance by electrolyte monitoring and potassium supplementation; (vi) the advent of specific antidotal therapy can reverse digitalis effect early in the evolution of toxicity [8,9]. The overall mortality rate may now be as low as <1% of patients taking the medication [9].

PHARMACOLOGY

While "digitalis" refers to a number of cardiac glycosides, this chapter will consider the effects of digoxin as most representative of current clinical prescribing. Occasionally, where appropriate, digitoxin's effects will be distinguished from those of digoxin.

The pharmacokinetics of absorption, distribution, and elimination of digoxin (Table 11.1) affect its pharmacologic and toxicologic activity in overdose. With digoxin tablets 50–80% absorption occurs through the intestine; food, antacids, malabsorption syndromes, and some medications, by changing gastrointestinal motility, interfere with digoxin's absorption. Digoxin in the form of an elixir or gelatin capsule is 80–100% absorbed. Two other agents in common use in Europe, beta-methyldigoxin and beta-acetyldigoxin have the advantage of complete oral absorption, but are thereafter hydrolyzed to digoxin, whose actions they replicate.

Digoxin has an apparent volume of distribution of 5–10 l/kg in newborns, 8.6–12.8 l/kg in older children and 5.0–7.5 l/kg body weight in adults [10]. Peak drug effect is seen 3–6 hours after a dose; digoxin has a distribution phase of 20–60 minutes in children but as long as 4–6 hours in adults [11]. It is

	Digoxin	**Digitoxin**
Absorption	40–90%	90–100%
Standard adult V_D (L/kg)	5–7	0.54
Onset of action	1.5–6.0 h (oral)	3–6 h (oral) 5–30 min (iv)
Peak half-life (hours)	30–45	>100
Duration of action (days)	3–6	14–21
Plasma protein binding	25%	95%
Elimination	kidneys (60–80%)	liver
Loading dose (mg)	0.75–1.25 (oral) 0.5–1.0 (iv)	0.8–1.2 (oral)
Daily maintenance dose (mg)	0.125–0.5	0.1
Therapeutic serum (ng/ml)	0.5–2.0	10–23
Toxic concentrations (ng/ml)	>2	>23

Table 11.1. *A comparison of pharmacokinetics of digoxin vs digitoxin (adapted from Ref. [52])*

eliminated with a half-life of 30–45 hours. Only 25% of a dose are bound to plasma proteins; up to 30% are secreted into bile. While digoxin is concentrated in both skeletal and cardiac muscle, other organs such as the kidneys and adrenals take up the drug as well.

Up to 90% of a therapeutic dose of digoxin are excreted unchanged in urine by filtration and tubular secretion [12]. In a patient with normal renal function, between 60–80% of a therapeutic dose of digoxin is excreted within 6–12 hours after ingestion. The elimination half-life of the drug is longer in neonates ($T_{1/2}$ 35–70 hours) than children and adults ($T_{1/2}$ 26–45 hours), related primarily to a marked increase in the renal clearance of digoxin with age [13]. The reader is referred to two recent reviews of the developmental aspects of the pharmacology, kinetics, and toxicity of digitalis in infants and children [10,14]. Digoxin's narrow therapeutic index (0.5–2.0 ng/ml) makes intoxication during the course of treatment a common occurrence. Comparison of the pharmacokinetic characteristics of digoxin versus digitoxin are shown in Table 11.1. Digitoxin has a much smaller volume of distribution, undergoes hepatic metabolism, and has a much longer elimination half-life compared to digoxin.

TOXIC DOSE AND CONCENTRATION

The usual maintenance dose of digoxin for an adult is 0.25–0.50 mg daily, giving a serum digoxin concentration <2.0 ng/ml. Patients with refractory atrial fibrillation may require higher doses to achieve a normal heart rhythm. Single digoxin ingestions of >4.0 mg in adults and >0.3 mg/kg in infants and children are almost always associated with significant toxicity. Serum digoxin concentrations of >2.0 ng/ml in adults, >2.5 ng/ml in older children, and >3.0–5.0 ng/ml in infants are often accompanied by symptoms and signs of toxicity. Corresponding toxic concentrations of digitoxin are those >23 ng/ml [11].

MECHANISMS OF TOXICITY

The actions of digitalis on membrane ion transport systems account for some but not all of its therapeutic and toxic effects. Digitalis interferes with the membrane-bound, ATPase dependent sodium/potassium exchange pump, leading to increased intracellular concentrations of sodium ion. This facilitates sodium–calcium exchange across the sarcolemmal membrane, leading to increased intracellular calcium available to the sarcoplasmic reticulum of the myocardial cell and an enhanced myocardial contractile state.

Concomitantly potassium transport across the cellular membrane is reduced, resulting in hyperkalemia. Dog studies have demonstrated a 25% decrement in active potassium transport at therapeutic digoxin doses and a 60% decrease below baseline levels at toxic doses [15]. These ionic changes are manifested electrophysiologically by a reduction in the resting potential during

phase IV of the depolarization–repolarization cycle (leading to increased automaticity and ectopic impulse activity). This results in a slowing of the rate of phase 0 depolarization, a decrease in the rate of conduction, a decrease in the amplitude of the action potential generated, and an acceleration of repolarization [16].

Several additional subcellular mechanisms of digitalis action are also known experimentally. Enhanced norepinephrine release and inhibited re-uptake at cardiac sympathetic nerve terminals is seen experimentally but has doubtful clinical relevance. However the antiadrenergic properties of digitalis at the atrioventricular node are thought to be contributory to its toxic effects of conduction block [16]. Digitalis also directly enhances the slow inward calcium flow through slow calcium channels, increasing inotropy but negatively affecting the propagation of impulses and depressing conduction. Also decreased intracellular pH, in response to increased intracellular calcium concentrations, may lead to enhanced hydrogen–sodium exchange, thereby augmenting the rise in intracellular sodium ion concentrations. Digoxin may also decrease the affinity of membrane phospholipids for calcium, making calcium more easily mobilized into myocardial cells promoting increased contractility.

Finally digitalis increases vagal tone directly, leading to negative chronotropic effects, a decrease of sinoatrial node depolarization, slowed conduction and increased refractoriness of both the sinoatrial and atrioventricular nodes.

The results of such ionic changes, neural effects, and indirect actions are both a decrease in maximum diastolic potential and a reduction in phase 4 depolarization in sinoatrial and atrioventricular conduction cells. In toxic amounts, therefore, digoxin depresses sinoatrial conduction and can even lead to sinoatrial exit block through both direct effects and through increased vagal tone. Through abnormally increased automaticity in pacemaker and Purkinje cells, triggered fascicular or ventricular tachyarrhythmias are also manifest [17].

Digoxin also causes emesis through central effects on chemoreceptors located in the area postrema in the medulla.

Generally digoxin and digitoxin are thought to be pharmacologically equivalent in potency. However, Joubert [18] observes that the pharmacodynamic properties of the different cardiac glycosides may be slightly different, based in part on differences in their lipophilic characteristics. More hydrophilic compounds (such as oubain and lanatoside C) may have increased effects on peripheral vagal tone and consequently may be associated with relatively more negative chronotropy. Lipophilic compounds (for example, digitoxin, meproscillarin) may be more able to penetrate the CNS and produce increased sympathetic tone, accounting for more positive inotropic effects. Digoxin is somewhere midway between lipophilic vs hydrophilic; thus it might cause relatively more nausea and vomiting (adverse vagal effects) than digitoxin. Use of digitoxin in turn might be associated with more instances of diarrhea (increased sympathetic tone) [18].

CLINICAL FEATURES

Host and agent susceptibility

Characteristics of the host and agent may impart particular vulnerabilities to digitalis. Adults and the elderly seem more susceptible to the toxic effects of digitalis than children [13]. Lewander et al. [19] reported on 41 pediatric cases of acute digitalis poisoning seen in 3 teaching hospitals over a 10-year period. Only 27% of cases, those with serum digoxin concentrations >2 ng/ml, developed any symptoms of toxicity; and none of the electrocardiographic changes seen, which were mostly bradycardia or AV block, were considered life-threatening. Nevertheless, other authors [10,14,20] have reviewed or reported case series of infants and children who experienced life-threatening symptoms or death after acute digoxin poisoning or chronic intoxication.

A variety of underlying medical disorders can increase the sensitivity of a patient to digoxin's toxic effects. Patients with impaired renal function eliminate digoxin slowly; liver disease delays the metabolism of digitoxin. Patients with advanced heart disease, myocarditis, myocardial infarction, complex congenital heart disease, recent cardiac surgery and acute/chronic cor pulmonale may be predisposed to digitalis toxicity. Patients with either hyperthyroidism or hypothyroidism and those with autonomic disturbances may be more sensitive to the effects of digoxin or have changes in the drug's volume of distribution or rate of elimination which predispose to toxic serum concentrations. Patients with hypokalemia due to total body potassium depletion as a result of the use of diuretics are also more susceptible to digitalis's toxic effects. Other electrolyte or acid/base disturbances may also increase the patient's sensitivity to the drug (see Table 11.2).

Drug interactions

The concomitant use of other medications may potentiate the effects of digitalis by a variety of mechanisms, leading to symptoms of toxicity. Quinidine inhibits the renal secretion of digoxin in a dose-dependent fashion and displaces it from binding sites in muscle and other tissue stores [13,21,22]. Digoxin serum concentrations may be doubled over a period of about five days when quinidine is given concomitantly; patients typically show clinical evidence of gastrointestinal and cardiac toxicity [23,24]. Spironolactone is structurally quite similar to digoxin and inhibits its binding to the Na/K ATPase membrane enzyme receptor in animals [25]; it may also delay its metabolism but does not seem to affect digoxin's serum concentration [24]. Its potassium-sparing diuretic effects may in fact be cardioprotective in a patient treated with both drugs. Other drugs, including verapamil, indomethacin and amiodarone, may act similarly to quinidine, potentiating digoxin's effects by blocking its renal filtration and/or secretion in a dose-dependent fashion [24].

Gastrointestinal effects

The earliest manifestations of digitalis toxicity, nausea and vomiting, are seen in up to 80% of cases and are neurally mediated. Both anorexia and weight loss are frequent features of chronic intoxication.

Patient-related factors	
	High dose
	The elderly patient
	Chronic renal insufficiency (Digoxin)
	Chronic hepatic failure (Digitoxin)
	History of congenital heart disease
	Recent myocardial infarction
	Recent cardiac surgery (mechanical and/or hypoperfusion injury)
	Myocarditis or cardiomyopathy
	Chronic pulmonary disease
	Acid-base disturbances
	Hypothyroidism/hyperthyroidism
	Cyanosis (hypoxemia)
Electrolyte abnormalities	
	Hyperkalemia
	Hypokalemia
	Hypercalcemia
	Hypomagnesemia
Drug–drug interactions	
	Spironolactone
	Calcium channel blockers
	Quinidine
	Sympathomimetic Agents
	Amiodarone

Table 11.2. *Factors associated with increased susceptibility to digitalis intoxication*

Cardiac arrhythmias

Cardiac effects from acute digoxin poisoning may be delayed as long as 6–8 hours, while the drug is being distributed to and concentrated in cardiac tissues. In toxic amounts digitalis causes variable electrophysiologic effects on the conduction system and cardiac muscle. Digitalis both stimulates ectopic centers and slows conduction. Such effects may create a unidirectional block which can generate ventricular arrhythmias as a result of junctional escape beats or circus movements through the Purkinje fibers and ventricular muscle. Kastor and Yurchak [26] described the sequential development of dysrhythmias due to digitalis in a patient with underlying atrial fibrillation as the progression from slowing of the ventricular response, to junctional escapes,

Ectopic rhythms	
	atrial fibrillation with slow ventricular response
	atrial fibrillation with regularization of ventricular response
	atrial flutter
	supraventricular tachycardia
	fascicular tachycardia
	atrioventricular junctional escape rhythms
	nonparoxysmal junctional tachycardia
	reciprocation
	multiform premature ventricular contractions
	ventricular bigeminy
	ventricular tachycardia
	ventricular fibrillation
	ventricular flutter
	"bidirectional" ventricular tachycardia
	parasystolic ventricular tachycardia
	ascicular tachycardia
	other ectopic rhythms
Depression of pacemakers	
	sinoatrial arrest
Depression of conduction	
	sinoatrial block
	1st atrioventricular block
	2nd atrioventricular block, Mobitz Type 1 (Wenckebach)
	complete atrioventricular block
	exit block
Ectopic rhythms with simultaneous depressed conduction	
	paroxysmal atrial tachycardia with block
	Wenckebach-type block with atrial fibrillation or flutter
Atrioventricular dissociation	
"Triggered automaticity"	

Table 11.3. *Digitalis-induced cardiac arrhythmias modified from Ref. [25].*

nonparoxysmal atrioventricular (nodal) tachycardia, acceleration of the junctional pacemaker, exit block of these pacemakers, and finally bidirectional tachycardia. Digitalis has on occasion caused atrial flutter and atrial fibrillation in overdose. Fisch and Knoebel [27] arranged the more typical arrhythmias seen according to the electrophysiologic mechanism of the disturbance, shown in Table 11.3.

In one prospective study of 931 hospitalized adults treated with digitalis, more than 50% of toxicity-related rhythm disturbances were of an atrioventricular junctional type [3]. A variety of conduction disturbances are also possible in digitalis poisoning. Interference with impulse propagation may occur in the sinoatrial or atrioventricular nodes or further down the His bundle; the consequence is a slowed ventricular response due to an entrance block.

Paroxysmal atrial tachycardia with block is a classic electrocardiographic finding of digitalis toxicity. Sinoatrial exit block is also seen. First or second degree atrioventricular block is the most common presentation of toxicity in children. Third degree or complete heart block is also seen in more severe intoxication.

Since the arrhythmias seen in digitalis intoxication are sometimes non-specific and may in fact reflect underlying heart disease, it is imprudent to rely on ECG disturbances alone to make the diagnosis. Rare arrhythmias, such as fascicular tachycardia, bidirectional ventricular tachycardia, ventricular bigeminy with alternating axis deviation, are highly suggestive of digitalis toxicity. Toxicity should also be suspected in patients whose ECGs exhibit the combination of enhanced automaticity and impaired conduction. In most cases, ECG findings must be judged in the context of the patient's other clinical findings and his/her serum digoxin concentration.

Neurologic effects

Acute digitalis poisoning commonly causes changes in consciousness early in the course of intoxication. Patients may be confused or may complain of headaches, fatigue, malaise and weakness for a period of days. Then they may develop progressive lethargy and obtundation. Coma is common in the severely intoxicated patient. Rarer complications include the onset of hallucinations, seizures, neuritis or transient blindness; patients may develop an acute psychosis. Visual changes (e.g. yellowish halos, scotomata, blurring, changes in color perception) and gastrointestinal complaints often herald the onset of intoxication and are also neurally-mediated.

Chronic toxicity

Many of the cardiac and neurologic signs of toxicity seen in the acute overdose with digoxin can also be found in the chronically intoxicated patient. These patients may become gradually ill with anorexia, fatigue, dehydration, and weight loss, mimicking a viral syndrome. Hypokalemia from the use of diuretics is a more common electrolyte disturbance in chronic digitalis intoxication. Visual disturbances, photophobia and "yellow vision" are sometimes seen. Confusion due to digitalis toxicity may be misdiagnosed as the onset of dementia. Rarely, patients may be acutely psychotic with hallucinations and disorientation. Neuralgias, paresthesias and gynecomastia may also be seen.

Poor prognostic factors

Those patients older than 55 years, of male sex, with underlying cardiac disease, with hyperkalemia, or with high-degree atrioventricular block have a worse prognosis. Patients overdosing on digitoxin are at risk for arrhythmias for several days, due to the drug's long half-life.

Fatalities

Death during digitalis poisoning usually results from ventricular fibrillation (65% of deaths), ventricular asystole (25% of deaths), or pump failure due to conduction block (10% of deaths) [11]. Mesenteric infarct also may occur, especially in the elderly, and may be fatal.

DIAGNOSIS

The diagnosis of digitalis toxicity continues to be problematic since the early signs and symptoms of toxicity are subtle, variable and non-specific; likewise ECG changes may be both non-specific and non-diagnostic and serum digoxin concentrations may not correlate well with clinical toxicity. There is a danger of misdiagnosis with digitalis intoxication frequently mistaken for influenza or dementia. Over-reliance on the stated ingested dose of digoxin may lead to erroneous judgments. As little as 5 mg of digoxin in a previously healthy adult or 2 mg digoxin in a previously healthy child has caused toxicity.

Laboratory measurements may aid in the diagnosis. Because of interference with the cellular Na/K pump, patients may have life-threatening hyperkalemia. However there is considerable overlap between therapeutic and toxic serum digoxin concentrations. Over-reliance on the serum digoxin concentration will lead to the erroneous over-diagnosis or under-diagnosis of digitalis intoxication. Serious arrhythmias have been associated with serum digoxin concentrations less than 3.0 ng/ml. However, life-threatening arrhythmias after acute overdoses are most commonly seen with post-distribution serum digoxin concentrations greater than 10 ng/ml. Additionally endogenous, glycoside-like substances have been found to cross-react with the antibody currently used in digoxin immunoassays in some infants and children (especially newborns), patients with liver disease, renal disease, and/or hypertension, and pregnant women leading to falsely elevated serum digoxin measurements. Such limitations in laboratory measurements argue for caution in the interpretation of a single serum digoxin concentration and for a need to correlate such findings with the patient's clinical and electrocardiographic findings.

MANAGEMENT

Patient stabilization

Of primary importance in the management of digitalis toxicity is, first, the need to stabilize the patient. Those patients experiencing cardiac arrest must be resuscitated with attention to adequate perfusion and ventilation.

Decontamination

In acute poisonings, decontamination of the patient can be useful in preventing further drug absorption. The role of ipecac-induced vomiting or orogastric lavage is controversial; increased vagal tone may potentiate digitalis-induced bradyarrhythmias, leading to asystole. Such exaggerated vagal effects are most dangerous at 4–6 hours after ingestion, when digitalis has been distributed to cardiac and other tissue sites. Since decontamination is most effective when performed within 60 minutes of ingestion, such a time limitation on the use of ipecac or lavage may mitigate against the danger of iatrogenic bradycardia.

Activated charcoal effectively adsorbs up to 40% of a single dose of digoxin if given within 60 minutes of the ingestion [28]. Since 30% of digoxin may be recirculated in bile, there is also a rationale for the use of multiple doses of activated charcoal given to the patient every 3–4 hours [29]; however it is doubtful that such multiple doses effect meaningful decreases in the total body burden of digitalis. While the resins, cholestyramine and colestipol, are capable of binding both digoxin and digitoxin [30], they have not been proven more efficacious than activated charcoal.

Digoxin-specific Fab antibody fragments

With supportive care only, patients acutely poisoned with digoxin have had mortality rates as high as 20% [5]. The introduction of digoxin-specific Fab antibody fragments has revolutionized the management of these patients. The reader is referred to excellent reviews of the clinical use of immunotherapy to treat intoxications [31,32].

The first animal experiments isolating digoxin-specific antibodies were carried out in rabbits by Butler and Chen in the 1960s [33]. Later studies demonstrated that such antibodies could: (i) reverse the digoxin-associated inhibition of potassium influx in human red blood cells, (ii) reverse the inhibitory effect of digoxin on canine myocardial Na/K ATPase, (iii) reverse the positive inotropic effects of digoxin on isolated myocardial strips, and (iv) reverse the toxic effects of digoxin on canine myocardial conduction tissue [34].

More specific, effective, and safer antibodies were created when digoxin-specific Fab fragments were made by the cleavage of the whole antibody with papain. These Fab fragments were found to be similarly effective in treating digoxin-induced dysrhythmias in cats [7].

Fab fragments have been found to retain the biological activity of whole antibodies but are more clinically suitable for use because: (i) Fab fragments have a larger volume of distribution than whole antibody and can more readily diffuse into interstitial tissue sites to reach digoxin-sensitive myocardial cells, (ii) Fab fragments, unlike whole antibodies, are readily excreted in urine either in free form or when bound to digitalis, and (iii) Fab fragments lack antigenicity induced by the whole antibody. Fab fragments work by binding free serum digoxin and digoxin in the interstitial space, which reduces the serum concen-

tration of free drug to near-zero; consequently cellular membrane digoxin-receptor equilibrium is displaced in the direction of dissociation.

Clinical use of Fab

Smith et al. [35] first described in 1976 the successful use of sheep-derived, digoxin-specific Fab antibody fragments (Fab) in the treatment of a 39-year-old patient who had ingested 22.5 mg of digoxin and thereafter suffered intractable hyperkalemia and progressive intraventricular conduction delays.

Fab treatment reversed the cardiac arrhythmias within minutes of the completion of Fab infusion; and the serum potassium fell to the normal range within 4 hours. Subsequently Smith and colleagues reported preliminary results of a multicenter trial in which 80% of 26 patients with advanced digoxin or digitoxin intoxication refractory to conventional therapy recovered completely with Fab treatment [36] The final report on the multicenter trial described 150 cases of life-threatening digitalis intoxication treated with Fab fragments [37]. Since the licensing of Fab fragments in the United States in 1986, a post-marketing surveillance study [38] of 717 adults who had received Fab fragments reported a partial or complete response rate in 74%, 14% in whom the response was not reported or uncertain, and 12% in whom there was no response. Of patients in the multicenter trial responding to Fab, 75% had at least some response by 60 minutes [37] Those patients who did not respond to Fab were generally either moribund prior to the onset of therapy, received an inadequate dose of Fab because of limited supply, had concomitant ingestion of other toxic medications, had severe compromising underlying medical conditions, or in retrospect, were not cases of digitalis intoxication.

The use of Fab in the treatment of massive acute digoxin poisoning in two children was first reported in 1982 [39,40]. In both cases conventional therapy, including ventricular pacing, failed to reverse ventricular fibrillation or progressive atrioventricular block; however the arrhythmias resolved within hours of an Fab infusion. In a review of 57 children enrolled in either the multicenter or post-marketing surveillance studies, almost 88% had partial or complete resolutions of both cardiac and extracardiac symptoms and signs of digitalis toxicity after Fab therapy [41]. Of 19 children in the multicenter study in whom a time to complete response to Fab was reported, 15 had achieved complete resolution of symptoms within 3 hours of the Fab infusion [20].

Indications for Fab

Fab fragments are now the mainstay of specific treatment for acute digitalis poisoning and chronic intoxication, acting to promote the rapid release of digoxin from cardiac binding receptors. Digoxin-specific Fab fragments are indicated for those patients with confirmed exposure to digitalis (either by known toxic dose or elevated serum concentration) who give evidence of life threatening arrhythmias and/or conduction defects, hyperkalemia, or hypoten-

sion. The earlier use of Fab has been advocated for those cases of digitalis poisoning in whom massive overdose is suspected despite the lack of life-threatening symptoms, and those in whom a rapidly progressive clinical deterioration precludes confirmation of the serum digitalis concentration.

Dosing of Fab

Fab is equally effective for both digoxin and digitoxin poisoning, and probably binds to active metabolites and other cardiac glycosides as well [42]. The dose is calculated based on total body drug load, calculated using either the estimated dose taken (in acute overdoses) or the steady-state serum concentration.

For serum digoxin concentrations (SDC in ng/ml):

$$\text{Digoxin Body Load} = \frac{5.6 \times \text{SDC} \times \text{body weight in kg}}{1000}$$

For serum digitoxin concentrations (SDtC in ng/ml):

$$\text{Digitoxin Body Load} = \frac{0.56 \times \text{SDtC} \times \text{body weight in kg}}{1000}$$

Each 40 mg of Fab fragments (1 vial) binds 0.6 mg of digoxin or digitoxin body load and so the total dose of Fab can be calculated accordingly. If the dose of digitalis taken is known, then the total body load can be calculated by multiplying that dose times the bioavailability of the oral drug:

$$\text{Digoxin Body Load} = \text{Digoxin Dose (mg)} \times (0.8)$$

$$\text{Digitoxin Body Load} = \text{Digitoxin Dose (mg)} \times (1.0)$$

If neither the dose of digoxin nor the serum digoxin concentration are known in a patient suffering life-threatening symptoms of digitalis poisoning, it is recommended that 800 mg of Fab fragments be administered empirically.

Time course after Fab fragments

Fab fragments are generally infused intravenously over 15–20 minutes. In two adult cases of acute digoxin overdose, gastrointestinal manifestations of toxicity abated during the Fab infusion; cardiac toxicity and hyperkalemia resolved completely within 30–60 minutes after the infusion [17,43]. Pharmacokinetic studies have demonstrated that 99% binding of free plasma digoxin occurs within 1 hour after the completion of Fab infusion [44]. If there is no resolution of the patient's symptoms and signs within 3–4 hours of Fab infusion, the clinician must consider that: (i) an inadequate dose of Fab has been given or (ii) there is an alternative explanation of the patient's clinical findings besides digitalis intoxication.

Smolarz et al. [45] studied the use of Fab in 34 toxic patients and calculated an elimination half-life for the Fab-digoxin complex of 20–30 hours. Some patients did have a rise in their free serum digoxin concentrations to 2–3 ng/ml 8–12 hours after the administration of Fab, presumably due to continued movement of digoxin from intracellular receptors to the intravascular space. Thus patients require close monitoring for recrudescence of cardiac symptoms attributable to a rebound in serum digoxin concentration, thereby requiring a second dose of Fab.

Adverse effects of Fab

Although allergic reactions to Fab appear to be rare, atopic patients or those who have received Fab previously would seem to be at particular risk. None of the 150 cases reported by Antman et al. [37] had evidence of an allergic reaction. Six of 717 patients (0.8%) in the post-marketing surveillance study had an apparent allergic reaction [39]. These reactions for the most part were limited to rashes, facial flushing and edema, or urticarial-type reactions; all responded to symptomatic therapy and no patient suffered anaphylaxis. None of the 57 children reported by Woolf [41] had allergic symptoms. The manufacturer also recommends skin-testing for allergic patients and others with previous hypersensitivity reactions. Pre-treatment with antihistamines or corticosteroids might be necessary in the face of positive skin-tests.

There are reports of patients whose low cardiac output or congestive heart failure was possibly exacerbated by the abrupt withdrawal of digitalis after Fab treatment [34] Hypokalemia has also been noted, such that serial serum potassium measurements are recommended for all patients for several days following Fab treatment. Problems of hypokalemia or exacerbations of congestive heart failure occurred in less than 10% of 150 adult patients treated with Fab [37] and in only 3% of 29 treated children [20]. Only 3% of the 717 patients studied by Hickey et al. [38] suffered recrudescing symptoms of digitalis toxicity; and they also calculated that the risk increased 6-fold when <50% of the estimated dose of Fab required had been administered to the patient.

Monitoring results of Fab

In large prospective studies of adults, Fab fragments have been found to be more than 84% effective in converting arrhythmias to a sinus rhythm [37]; studies of children documented an 85% overall success rate [41]. Close clinical monitoring of patient's cardiac status including pulse, blood pressure, and ECG, after Fab administration is suggested. Recrudescence of atrioventricular block or other arrhythmias in adults has occurred up to 72 hours after therapy with Fab, requiring a second dose of the antidote.

Fab fragments affect commercially-available digoxin assay kits which measure both the free (digoxin available for receptor binding) and total (free digoxin plus that bound to Fab) digoxin such that the serum digoxin concentration rises

rapidly after Fab infusion, most of which is biologically inactive [46,47]. Monitoring the patient's serum digoxin concentration after the administration of Fab is not possible until the Fab-bound digoxin is cleared from the blood, usually within 5 days in a patient without underlying renal failure. Newer more accurate methods using ultrafiltration coupled with a fluorescence polarization immunoassay, are able to distinguish between free and bound digoxin which is useful in the monitoring of patients. These tests are under commercial development [48,49]. The serial measurement of free digoxin after Fab treatment would be particularly useful in monitoring those patients with renal insufficiency, or those with incomplete responses or recrudescing symptoms after Fab therapy [49].

Other pharmacotherapies

Other supportive pharmacotherapy in digitalis poisoning may include antiarrhythmic agents such as lidocaine and phenytoin. Both procainamide and β-adrenergic blocking agents can have negative effects on cardiac conduction and contractility, and are thus best avoided. A very short-acting specific β-blocker, such as esmolol, may be appropriate early on in the course of a severely intoxicated patient, who is experiencing negative inotropy and catecholamine-induced automaticity [9].

Quinidine further delays conduction, can be proarrhythmic itself, and prolongs digitalis toxicity; bretylium tosylate, by stimulating the release of catecholamines, may in fact worsen digitalis-associated arrhythmias and is also not recommended.

Atropine can be an effective first-line drug for bradyarrhythmias due to mild overdoses; but it is relatively ineffective in serious digitalis intoxication. Magnesium sulfate infusions or amiodarone have also been found to control refractory ventricular fibrillation in two isolated cases; however in neither case was Fab therapy used initially in managing the patient [50,51].

Potassium infusion can be helpful in controlling ventricular ectopy from digoxin toxicity in patients with hypokalemia, even when serum potassium levels are in the "normal" range. However potassium should be used cautiously in such patients, with the serial monitoring of serum levels, ECG, and cardiac status. It is contraindicated in those suffering from one-time digoxin overdose who may be developing progressive hyperkalemia, as well as in those with renal insufficiency.

Cardioversion

Direct current cardioversion may be safe and successful in those patients without digitalis-induced arrhythmias, especially if low energy levels are used. Since the presence of even therapeutic amounts of digoxin can put the patient at some risk for ventricular fibrillation during cardioversion, prophylactic administration of lidocaine prior to cardioversion may be advisable.

Cardioversion can be hazardous if used in those patients with severe digitalis poisoning and progressive ectopic rhythms.

Ventricular pacing

Ventricular pacing has also been advocated for those patients with life-threatening arrhythmias, most often those with atropine-resistant severe brady-arrhythmias secondary to high-degree block. However, some researchers have recently questioned the utility of pacing in light of the availability of Fab fragments. Taboulet et al. [52] discovered that 36% of 39 patients with digitoxin intoxication who received ventricular pacing experienced iatrogenic complications (pacing-induced arrhythmias, pacing defects, or infections) secondary to this intervention; these complications were fatal in 5 of the patients. Thus they argue that electrode placement, manipulation or ventricular pacing itself lower the fibrillatory threshold, placing the patient at risk for serious arrhythmias. Also they suggest that the practice of briefly slowing the rate of pacing to study the underlying arrhythmia may place the patient at risk for a degenerating rhythm or sudden asystole. Some clinicians have therefore advocated that pacing be considered only as a last resort after pharmacotherapy and immunotherapy have failed or if there is an unacceptable delay in obtaining Fab [11,53].

Enhanced elimination

Both hemodialysis and hemoperfusion remove only a small fraction of a body load of digoxin and are ineffective in improving a patient's course. Hemodialysis would effectively treat the hyperkalemia associated with digitalis intoxication; however Fab also readily reverses the hyperkalemia associated with digoxin toxicity.

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12. Antihypertensive and anti-anginal drugs

INTRODUCTION

Acute poisoning with antihypertensive and anti-anginal drugs is uncommon. Hypotension and dysrhythmias are the main complications so most cases of deliberate overdose will require monitoring in an intensive care facility. Most of the problems result from deliberate or accidental overdose but similar effects can occur in "at risk" patients at standard dosage.

Emesis or lavage may be helpful if a large overdose has been taken. Sudden loss of consciousness has been described with clonidine and vomiting is best avoided in this type of poisoning. Activated charcoal when administered at adequate dose (10 times the weight of the suspected overdose) is an effective adsorbent for the drugs under discussion.

In most cases, hypotension can be treated using simple measures such as intravenous saline and elevating the legs. Symptomatic bradycardia often responds to atropine but when combined with hypotension and low cardiac output, an inotropic agent such as dopamine, dobutamine or noradrenaline may be required. Arrhythmias due to hypokalemia require electrolyte replacement while glucose/insulin, cation exchange resins and hemodialysis may be required for hyperkalemia. Electrical pacing is indicated for severe sustained arrhythmias.

This review discusses the main clinical features and management of the antihypertensive–anti-anginal agents in common clinical overdose.

β-ADRENOCEPTOR ANTAGONISTS

Clinical effects

Although the most common adverse effects of β-adrenoceptor antagonists (β-blockers) in clinical practice occur as a result of β_2-antagonism airways obstruction, reduced peripheral blood flow and impaired glucose homeostasis,

their principal effects in overdose are on the cardiovascular and central nervous systems [1].

Cardiovascular effects. The main cardiovascular effects are hypotension and disorders of cardiac conduction. Sinus bradycardia and lengthening of the PR interval are the most frequently observed electrocardiographic abnormalities but with massive overdoses, high-grade atrioventricular block, widening of the QRS complex and asystole can occur.

Sotalol, which has additional type III antiarrhythmic activity, can cause marked prolongation of the QT interval in overdose and predispose to ventricular dysrhythmias [2,3]. Cardiogenic shock and pulmonary oedema may result from impaired cardiac contractility especially in patients with pre-existing myocardial disease. This can develop rapidly in patients who have taken an overdose of propranolol and who were almost asymptomatic immediately beforehand [4]. Cardioselective β-adrenoceptor antagonists are less likely to cause life-threatening cardiac effects than non-selective drugs. Sinus bradycardia was the only reported adverse effect of bisoprolol, a highly selective β_1-adrenoceptor antagonist when taken in overdose [5]. Pindolol, a drug with partial agonist activity can cause hypertension and tachycardia in overdose, and hypotension is unusual even with large doses.

Central nervous system (CNS) effects. CNS effects, particularly convulsions, are more commonly associated with strongly lipid soluble drugs, for example metoprolol, oxprenolol and propranolol, than those which are largely water soluble, such as atenolol and nadolol. Seizures usually occur in patients with reduced cardiac output but have been reported without major impairment of cardiac function, although impaired cardiac conduction frequently antedates their onset [6]. In patients who have taken oxprenolol in overdose, coma frequently preceded the convulsions [7]. Other CNS effects which can occur following an overdose with β-adrenoceptor antagonists include lethargy, amnesia, apnoea and dilated pupils. All may appear suddenly and with little warning [8].

Biochemical abnormalities. Hyperkalemia and hypoglycemia can sometimes cause problems in overdosage. Increases in serum potassium occur as a result of antagonism of the β_2-receptors in the liver and skeletal muscle. β-blockers do not increase plasma insulin levels at therapeutic doses [9] but β_2-receptors are involved with insulin secretion, and in overdosage clinically important hypoglycemia has been described. β-adrenoceptor antagonists are frequently taken with other drugs and these can cause additional problems in overdosed patients. Clinically important interactions have been described with verapamil, disopyramide, lignocaine and tocainide [10] resulting in cardiac failure, hypotension, bradycardia, atrioventricular block and asystole.

Plasma concentrations can be used to support the diagnosis and to confirm that large doses have been taken. Propranolol plasma levels relate poorly to the degree of β-adrenoceptor blockade because of the formation of an active metabolite, 4-hydroxypropranolol [11]. However, in overdose because this metabolic pathway is saturated, plasma levels of the parent compound more accurately reflect the severity of the overdose.

Management

Early diagnosis of overdosage with β-adrenoceptor antagonists is essential since delay in treatment can prove fatal. Patients should be admitted to an intensive care unit where blood pressure, cardiac rhythm and respiratory rate can be carefully monitored. Hyperkalemia and hypoglycemia should be treated if necessary. Gastric lavage and activated charcoal are probably of value if undertaken within four hours of drug overdose. However gastric lavage has been associated with excessive vagal stimulation which has resulted in asystole, unconsciousness and death in patients who have taken large doses of β-adrenoceptor antagonists. If gastric lavage is considered necessary then pretreatment with atropine is advised [12].

Emesis is best avoided as apnoea, convulsions and coma can occur suddenly. A variety of agents have been used to reverse the effects of these drugs at the β-receptor. Isoprenaline (up to 200 μg/min), which has agonist activity at the β_1- and β_2-receptors, has been used to reverse the bradycardia and conduction abnormalities associated with overdose, but it is usually ineffective in reversing hypertension. At present, glucagon (50 μg/kg intravenous bolus followed by 70 μg/kg/h) seems to be the most effective drug for treating β-blocker overdosage [13,14]. It has no direct effects on the β-receptor but increases myocardial contractility by stimulating cyclic AMP within myocardial cells. Continued administration of glucagon can cause major metabolic problems such as hyperglycemia, hypokalemia and hypercalcemia which require careful monitoring and correction [14]. Prenalterol (up to 40 mg in the first hour and 130 mg for the next 24 hours), a β_1 adrenoceptor partial agonist, has been used at high dose intravenously to correct the hypotension resulting from massive overdoses with atenolol, metoprolol and propranolol [15]. Its main indication at present would be for severe overdoses not responding to glucagon or adrenaline. Recent animal data suggest that milrinone, a phosphodiesterase inhibitor, may be as effective as glucagon [16] and amrinone has been successfully employed to treat a labetalol overdose [17].

Other measures which have been used to improve cardiac function following a severe overdose with β adrenoceptor antagonists include atropine to increase heart rate, inotropic agents dopamine, dobutamine and noradrenaline, cardiac pacing and intra-aortic balloon pumps [18] to improve cardiac output. Diazepam intravenously is probably the best drug to control convulsions and a β_2-agonist such as salbutamol or terbutaline by inhalation for drug-induced bronchospasm.

CALCIUM CHANNEL ANTAGONISTS

Clinical effects

Cardiovascular effects. The clinical effects of the three main groups of calcium antagonists, the papaverine derivatives (example verapamil), the benzo-

thiazepines (example diltiazem) and the dihydropyridines (example nifedipine) are different because of their different effects on cardiac contractility, conduction and vascular smooth muscle. Because of these differences, the three groups will be discussed separately. Verapamil and related compounds cause the most serious problems in overdose.

(1) *Verapamil.* Massive verapamil overdose produces effects which are due to exaggeration of the well known pharmacological actions. CNS effects also commonly occur. Several case reports of verapamil poisoning were recently published [19–22]. Bradycardia and conduction abnormalities are the most commonly observed clinical signs. The conduction abnormalities include varying degrees of atrioventricular, junctional or idioventricular rhythms, bundle branch blocks and asystole [19,23]. Hypotension occurs in most verapamil overdoses usually one or two hours after drug ingestion, although patients taking a large overdose of verapamil may rapidly deteriorate with profound hypotension, complete heart block, metabolic acidosis and anuria [24]. In a series of thirty-eight patients poisoned with verapamil, 9 had systolic blood pressures below 100 mmHg and 5 had systolic blood pressures less than 60 mmHg [25]. In general, verapamil produces less vasodilatation than nifedipine, and hypotension is mainly due to the negative chronotropic and inotropic effects on the heart. CNS effects, in large part due to impaired cerebral perfusion, can result in a decreased level of consciousness, convulsions and coma. Non-specific features such as nausea, vomiting, lightheadedness and headache may also occur.

(2) *Diltiazem.* Reports on a small number of cases of diltiazem overdosage are available. As with verapamil, hypotension and disturbances of atrioventricular conduction with junctional escape rhythms are the abnormalities most frequently observed [26–28]. CNS effects such as confusion and lethargy have been reported as well as abdominal pain, nausea and vomiting [28]. A single case of non-cardiogenic pulmonary oedema following a large dose of verapamil has been described [29].

(3) *Nifedipine.* As a result of marked vasodilatation, the main effect seen in deliberate overdose is hypotension. Heart rate tends to increase and arrhythmias are uncommon [30,31]. However cardiogenic shock and idioventricular rhythms have been reported in patients with underlying heart disease [31], and heart block followed by asystole has been described in a 14-month-old child after ingestion of 800 mg nifedipine [32].

Central nervous system toxicity. Overdoses of calcium channel entry blockers often produce mental changes. Confusion, agitation, lethargy, dizziness and slurred speech are the most common. Seizures have rarely been reported.

Gastrointestinal toxicity. Nausea and vomiting often occur in overdose with calcium antagonists. Verapamil commonly causes constipation even at therapeutic doses and has been associated with paralytic ileus and small bowel obstruction.

Hyperglycemia is a common finding in drug overdoses with nifedipine, diltiazem and verapamil. The effect is short-lived and rarely lasts more than twenty four hours. Insulin administration has occasionally been used [21,34].

Management

Treatment of a severe overdose with a calcium channel antagonist involves reducing absorption and attempting to counteract the effects of the drug on conduction, myocardial contractility and vascular tone. Seriously poisoned patients require cardiac monitoring, an intravenous line and oxygen therapy. Respiratory and CNS depression should be sought for and managed if necessary. Hypotension, if severe, requires the insertion of a Swan–Ganz catheter. Intravenous fluids with or without inotropic agents may be required. The usual methods to reduce gastrointestinal absorption, emesis, lavage or activated charcoal, are probably of value within four hours of drug administration but the physiochemical characteristics of calcium channel blockers mean that extra corporeal clearance systems are unlikely to be of value. Some authors have recommended polyethylene glycol as the treatment of first choice to reduce absorption [35]. A variety of agents have been used to improve cardiac contractility, atrioventricular conduction and to increase blood pressure. Most of the information on the use of these agents relates to verapamil overdose.

Calcium. Although calcium administered intravenously has been shown to reverse the hypotension due to verapamil when used to treat supraventricular tachycardia [34,36], the ability of calcium to reverse the hypotension associated with drug overdose is much less clear cut. In patients overdosed with calcium channel antagonists, calcium may reverse myocardial depression and occasionally increase heart rate and improve atrioventricular conduction. There are several reports documenting apparent benefit of calcium salts following verapamil, diltiazem and occasionally nifedipine overdosage [36–38]. There are also, however, a few case reports of patients with severe poisoning who fail to respond to this therapy [27,40,41]. It has been suggested that calcium chloride is more effective and more reliable in increasing extracellular calcium than calcium gluconate [41], although the optimum dose of calcium chloride is unknown. Intravenous calcium, however, appears to be most effective when administered in doses greater than 1 g, and up to 4 g may be necessary in severe verapamil overdose. In general, calcium has been shown to improve cardiac contractility and cardiac conduction in some patients but is unlikely to have a major effect on peripheral resistance and hence blood pressure.

Atropine. Atropine has been ineffective in treating heart block and bradycardia associated with verapamil overdose although another anticholinergic drug methylscopolamine was effective in abolishing ventricular escape rhythms in a case of verapamil toxicity [24]. Anticholinergic drugs do not appear to improve impaired atrioventricular conduction [41].

β-Agonists. A variety of β-adrenoceptor agonists have been used to stimulate the force of myocardial contraction, to increase heart rate and elevate blood pressure. In some cases, isoprenaline increased heart rate [44] and had a slight effect on blood pressure [43]. In other reports, however, isoprenaline had no useful clinical effect [23,34]. β_2-stimulation occurring at high dose can cause reductions in blood pressure and β_2-stimulation can also increase myocardial

oxygen demand. The role of β-agonists in calcium antagonist overdose is doubtful.

Glucagon. Glucagon is a polypeptide hormone which has positive inotropic and chronotropic actions unaffected by noradrenaline depletion or by adrenergic blockade. It increases cAMP levels by stimulating adenylate cyclase and probably by altering transmembrane calcium flux [45]. In a case of verapamil poisoning, Crump et al. [40] were unable to demonstrate any improvement in a case of severe verapamil poisoning after multiple interventions which included 10 mg glucagon. In contrast, however, increases in blood pressure with glucagon were observed in a 27-year-old man with hypotension following a nifedipine overdose.

4-aminopyridine. 4-aminopyridine is an antagonist of non-depolarising neuro-muscular antagonists which acts by inhibiting voltage-dependent potassium channels and facilitating the entry of calcium into cells [46]. Early animal experiments appeared successful [47] and in one case report, a patient who failed to respond to intravenous atropine, calcium and isoprenaline, converted to sinus rhythm following 10 mg 4-aminopyridine intravenously [43]. Repeated boluses may be necessary because the elimination half-life of 4-aminopyridine is substantially shorter than that of most calcium channel antagonists [46].

Methods used to increase drug removal. There appears to be no useful role for methods to increase drug elimination. Clinical reports indicate no benefit from hemodialysis, hemoperfusion or multiple dose activated charcoal to enhance the removal of calcium antagonists in overdose [43,48–50].

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Clinical effects

Angiotensin converting enzyme inhibitors appear to be remarkably safe when taken in overdose by healthy adults [51–53]. The severity of hypotension is related more to the degree of activation of the renin angiotensin system before drug administration than the dose of the drug [54]. Patients who have been receiving large doses of diuretics for congestive heart failure are therefore at greatest risk. Hyperkalemia, a relatively common finding with chronic therapy, is rare following deliberate drug overdose [55]. The patient in this case report had congestive heart failure and was taking spironolactone.

In most cases of deliberate overdose, hypotension is the only important clinical effect [56,57] although a single death has been recorded in a 75-year-old man following 1100 mg captopril [58].

The management of a patient with an overdose of an angiotensin-converting-enzyme inhibitor is largely supportive. Asymptomatic patients do not require active treatment but should be observed until the blood pressure returns to normal. For more severe symptomatic hypotension, intravenous saline is usually all that is needed, and angiotensin II is rarely if ever required

although it may be the treatment of choice in anuric patients [59]. Treatment of hyperkalemia with glucose-insulin, exchange resins and potassium restriction is sometimes necessary, usually only in patients with renal impairment who have been receiving potassium supplements and/or potassium sparing diuretics. There are a variety of reports relating to the value of naloxone as a method of increasing blood pressure. Ajavi et al. [60] suggested beneficial effects while Barr et al. [57] failed to reverse captopril-induced hypotension with naloxone.

CENTRALLY-ACTING ALPHA-ADRENOCEPTOR AGONISTS

Clinical features of drug overdose

The two main effects of the centrally-acting α-agonists, clonidine, methyl-dopa and guanabenz are hypotension and sedation. Hypotension occurs as a result of exaggerated central alpha adrenoceptor stimulation, although hypertension may sometimes occur due to increased peripheral α_2 stimulation. Centrally acting agents depress the central nervous system at therapeutic doses but especially in deliberate drug overdose. Sedation and dry mouth occur secondary to reduced central noradrenergic activity.

Clonidine. Clonidine at high dose causes drowsiness, respiratory depression, apnoea and coma. The picture of miosis, coma and respiratory depression is common and resembles narcotic overdose. A phenothiazine-like condition with dilated unresponsive pupils, hypotonia, hypothermia and depressed reflexes has also been described [61]. In the early stages after a clonidine overdose, bradycardia and hypotension are the main cardiovascular features. In the later stages, elevated blood pressure and atrioventricular blockade are more likely to occur.

Methyl-dopa. Acute overdose with methyl-dopa resembles that of a clonidine overdose, with symptoms such as hypotension, bradycardia, atrioventricular conduction abnormalities, hypothermia, dry mouth and coma [62]. Unlike clonidine, extrapyramidal effects are sometimes seen: bradykinesia, rigidity and gait disturbances together with a variety of autoimmune effects, hemolytic anemia, cholestatic hepatitis and myocarditis. These adverse effects are more likely to occur with chronic therapy.

Guanabenz. The few reports on overdose with guanabenz suggest that the features resemble clonidine overdose and run a short uneventful course.

Management

Patients with a suspected overdose of centrally-acting drugs should be admitted to an intensive care unit. Careful monitoring of respiratory function is essential since coma and apnoea can occur suddenly. Assisted ventilation is required for severe hypoventilation or apnoea. Electrocardiographic monitor-

ing is indicated for the more severe overdoses to detect cardiac dysrhythmias and heart block [63].

Hypotension should be managed initially by placing the patient in the Trendelenburg position and giving intravenous saline. Dopamine (5–10 μg/kg/min) or noradrenaline (8–12 μg/min) are occasionally necessary in severe unresponsive hypotension. Tolazoline (10 mg intravenous boluses up to 40 mg) is a central α-adrenoceptor antagonist which has been used to treat the hypotension and bradycardia due to clonidine overdose unresponsive to other measures. Worsening of hypotension has been described and there are major doubts about the value of this form of therapy. Bradycardia often responds to atropine (0.5–1.0 mg) although in most situations specific therapy is not indicated. Occasionally hypertension may require treatment and sodium nitroprusside (20–40 mg/min), sublingual nifedipine [64], and phentolamine [65], have been employed to lower blood pressure.

Naloxone has been used to treat episodes of coma with apnoea associated with clonidine overdose [66]. Its value has not been established [67] and rebound hypertension has been described if the drug is suddenly withdrawn. Intravenous diazepam is useful to control convulsions.

ALPHA-ADRENOCEPTOR ANTAGONISTS

Clinical features

The effects seen with an overdose of an α-adrenoceptor antagonist are due to exaggerated pharmacological activity [68]. The principal effect is therefore hypotension which is most marked in the upright position. Although non-selective α-adrenoceptor antagonists such as indoramin, phenoxybenzamine and phentolamine are more likely to cause postural hypotension at therapeutic doses than selective drugs such as prazosin, doxazosin or terazosin, at high dose selectivity is lost and postural hypotension is a prominent feature with all α-blockers. Other features include dyspnoea, headache, paraesthesia, sweating, nasal congestion, vertigo and generalised weakness. Although sinus tachycardia usually accompanies the decreases in blood pressure, tachyarrhythmias have rarely been reported [69].

Management

Apart from standard methods to reduce further drug absorption in large overdoses, treatment should be primarily aimed at correcting the fall in blood pressure. Discontinuation of the drug and maintaining the patient in the Trendelenberg position is all that is needed in the majority of cases. Pressor agents are best avoided, especially noradrenaline, since exaggerated responses are likely to occur [70].

DIRECT ACTING VASODILATOR DRUGS

These drugs act directly on vascular smooth muscle of arteries (hydralazine, diazoxide and minoxidil), veins (nitrates) or on both arteries and veins (sodium nitroprusside). Hydralazine probably also has some indirect inotropic effect causing a marked increase in cardiac output with little change in arterial pressure unless combined with β-adrenoceptor antagonists.

Clinical features

Arteriolar dilators. Hypotension is the main adverse effect of overdoses with hydralazine, diazoxide and minoxidil especially if combined with β-adrenoceptor antagonists and diuretics. Hyperglycemia can also occur with diazoxide and to a lesser degree with minoxidil.

Nitroprusside. Early signs of nitroprusside toxicity are metabolic acidosis [71] and loss of the antihypertensive effect [72]. Long-term administration can cause thiocyanate toxicity especially in patients with hepatic or renal impairment [73]. Symptoms associated with this are muscle fatigue, nausea, vomiting, confusion, hallucinations, convulsions, coma and death. Reversible hypothyroidism may also occur. On the other hand, cyanide production can cause hypotension, bradycardia, ventricular dysrhythmias and progressive cardiorespiratory failure. Important central nervous system effects have also been reported [74,75]. These include headache, vomiting, agitation leading to stupor, convulsions and death. Red cell cyanide and thiocyanate levels relate well to the different symptom complexes, and serious toxicity has been reported with cyanide levels of 2.5 mg/ml and above and thiocyanate levels greater than 12 mg/dl [75,76].

Nitrates. Nitrate vasodilators, glyceryl trinitrate, isosorbide mononitrate and dinitrate, mainly affect the veins although at high dose significant arteriolar dilatation may also occur. Vasodilator effects of a nitrate overdose range from headache, lightheadedness and flushing of the skin to sweating, profound hypotension and syncope. Cyanosis of the lips and mucous membranes is uncommon and suggests significant methemoglobinemia. This clearly reduces the oxygen-carrying capacity of the blood and can cause worsening of existing heart and lung disease. Levels of methemoglobin between 30 and 50 per cent are associated with tachypnoea, tachycardia and mild dyspnoea, levels between 50 and 70 per cent give rise to respiratory depression, convulsions and dysrhythmias while levels above 70 per cent are usually incompatible with life. Metabolic acidosis may also be present in severe cases.

Management

Arteriolar dilators. The treatment of drug overdose is discontinuation of the drug and supportive measures. Hyperglycemia may occasionally require treatment with insulin.

Nitroprusside. If nitroprusside toxicity is suspected, the infusion should be stopped and careful monitoring of blood pressure, heart rate and urinary output initiated. Occasionally intubation and assisted ventilation may be required if there is marked respiratory depression and pressor agents (dopamine or noradrenaline) may be required for severe persistent hypotension. If there is evidence of cyanide toxicity the recommendations of Chapter 26 should be adhered to.

Nitrates. Cardiac and respiratory monitoring is required in severe overdose and in patients with cardiac or pulmonary disease. Patients should receive 100% oxygen and intravenous methylene blue if clinically significant methemoglobinemia is suspected or confirmed [77]. Hypotension usually responds to elevation of the legs and intravenous fluids but dopamine may sometimes be necessary.

DIURETICS

For practical purposes diuretics can be divided into three main groups — the loop diuretics, thiazide diuretics and the potassium-sparing diuretics. Thiazide diuretics are the most commonly used diuretics in the management of hypertension although they are rarely needed with potassium-sparing agents to maintain serum potassium. Loop diuretics are used in the management of hypertension unless combined with angiotensin inhibiting enzyme inhibitors and vasodilator drugs.

Clinical features

Loop diuretics. Acute overdoses can result in lethargy and coma within a few hours of ingestion even in the absence of dehydration and electrolyte disturbance. The mechanism is unknown. The major electrolyte disturbances are hyponatremia, hypokalemia and hypomagnesemia which may predispose to serious ventricular arrhythmias [78,79]. Encephalopathy and hyperglycemia have been observed with high doses of bumetanide [80] and hypoglycemia has been reported with high dose ethacrynic acid. In contrast, hypoglycemia has been described in uremic patients. Gastrointestinal bleeding has been reported following intravenous administration of ethacrynic acid and frusemide in uremic patients.

Thiazide diuretics. Clinical features are similar to those seen with an overdose of loop diuretic, namely lethargy, dehydration and electrolyte disturbances, especially reduced sodium magnesium and sodium. Orthostatic hypotension, pancreatitis, hypercalcemia and thrombocytopenia have also been described.

Management

The mainstay of treatment for overdoses with thiazide and loop diuretics is fluid and electrolyte replacement. Intravenous saline with potassium and probably magnesium is all that is required in most cases. Methods to reduce

gut absorption, i.e. emesis, gastric lavage or activated charcoal, are of limited value and laxatives are contraindicated as they tend to worsen fluid and electrolyte loss.

In severe cases, ECG monitoring, maintenance of respiration and treatment of severe hypotension with pressor agents may be required. Hypertonic saline should be avoided as severe neurological damage has been reported. Potassium should be given slowly with careful plasma level and ECG monitoring. Intravenous glucose is required for hyperglycemia and insulin may be needed for severe hyperglycemia.

POTASSIUM-SPARING DIURETICS

Clinical features

Most clinical features of overdosage are related to hyperkalemia. The main features are muscle weakness, paraesthesia, bradycardia, hypotension and electrocardiographic abnormalities. Commonly observed abnormalities on the ECG include tall peaked T waves, widening of the QRS complex, prolonged PR interval, reduced R wave, ST segment depression and lengthening of the PR interval [81]. Gastrointestinal symptoms are also prominent and include nausea, vomiting, anorexia, abdominal pain and occasionally gastrointestinal bleeding. Angina pectoris, cardiac arrhythmias, visual disturbances and metabolic acidosis may also occur.

Management

Other medication which can worsen hyperkalemia, such as potassium supplements, β-adrenoceptor antagonists, angiotensin converting enzyme inhibitors and non-steroidal anti-inflammatory drugs, should be stopped. Hyperkalemia causing important ECG abnormalities and/or a serum potassium greater than 7.0 mmol/l requires emergency treatment. Possible treatments include potassium restriction, glucose/insulin and cation exchange resins. In resistant cases peritoneal or hemodialysis may be required. The response to these therapies should be assessed by ECG monitoring and serial electrolyte measurement.

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13. Minor analgesics and non-steroidal anti-inflammatory drugs

INTRODUCTION

Acute poisonings due to minor analgesics are very frequent even though the major culprit is no longer aspirin, but paracetamol (acetaminophen) due to changing trends of use. By contrast, non-steroidal anti-inflammatory drugs which induce so many and potentially severe side effects following medical prescription, are seldom involved as a cause of acute poisoning.

ASPIRIN

Acute poisonings due to aspirin (intentional or accidental) ingestion were frequent in the past and have resulted in many deaths [1]. The recent trend is a steady decrease in aspirin acute poisonings, greatly due to the introduction and increasingly wider use of paracetamol, even though over 22,000 phone calls relating to aspirin overdose were still recently recorded by poison control centers in the US [2]. This steadily decreasing trend has even led Chan [3] to suggest that salicylates should no longer be included in the systematic general screening of acutely poisoned patients upon hospital admission.

Few case reports of acute salicylate poisoning have been published in the recent past, giving further support to the view that aspirin is less and less often involved in severe or "remarkable" human poisonings. Children are typically at a higher risk of aspirin toxicity [1]. A 3-month-old girl developed a severe salicylate poisoning with nausea and vomiting, metabolic acidosis and convulsions after topical applications of a 4% salicylate formulation for the treatment of ichthyosis [4]. A 9-month-old boy presented with vomiting 30 minutes after the accidental ingestion of 20 ml of a traditional medicine containing methyl salicylate. He suffered from recurring convulsions [5].

Salicylate poisoning in the elderly may be either induced by lower doses than in adults (hence the advice to use smaller therapeutic doses) or associated with unusual clinical features, as recently reviewed [6]. Several recent case reports illustrated these specificities. Rodin [7] described one case of acute hemiparesia in a 78-year-old woman after the ingestion of approximately 4 g salicylates over

48 hours. The patient recovered uneventfully within 3 days. A 82-year-old woman used to ingest large amounts of bismuth sub-salicylate to alleviate abdominal pain [8]. She developed anorexia, confusion, dehydration, and fatal pulmonary edema. Her salicylate blood levels were 46 mg/dl. Another 78-year-old woman was admitted to the hospital because of confusion, dysarthria, agitation and hearing loss [9]. She had a metabolic acidosis compensated by respiratory alcalosis, and her salicylate blood level was 82 mg/dl. Her recent uncontrolled ingestion of aspirin was recognized and she fully recovered after supportive treatment. A 72-year-old man with severe renal insufficiency, diabetes and psoriasis was given daily topical applications of a pharmaceutical cream containing 10% salicylic acid over 80% of his body surface [10]. This amounted to 240 g salicylic acid for 3–4 weeks. He was admitted to the hospital with mental confusion and asthenia. His salicylate blood level was 3.2 mM/l and his glucose blood levels between 1.8 and 2.3 mM/l remained low despite glucose administration. He only fully recovered after cutaneous decontamination, hemodialysis and intravenous glucose.

Another report indicates that topical application of salicylates can result in severe poisoning [11]: a 42-year-old female patient received daily topical applications of 50 g of a pharmaceutical formulation containing 10% salicylic acid on the trunk and limbs, for 10 consecutive days. She developed agitation, tachycardia, hyperthermia, and her salicylate blood level was 2.6 mM/l.

Several unusual aspirin intoxications were recently reported in adults. Pond [12] described two patients with ARDS and a late diagnosis of salicylate chronic intoxication. A 44-year-old female patient with scleroderma and Sjögren's syndrome, developed unconsciousness, acute renal failure, rhabdomyolysis and metabolic acidosis, after several months of 3–4 g aspirin daily ingestion. She fully recovered after completion of hemodialysis. The role, if any, of underlying diseases is unknown [13].

An unusual case report of suicide attempt involving aspirin was reported in a 43-year-old woman who self-administered approximately 700 aspirin tablets dissolved in water, in enema form [14]. The patient became progressively acidemic and developed cardiac arrest and chronic hypoxic encephalopathy resulting in a coma for more than one year. As rectal absorption of aspirin is very slow, the administration of activated charcoal via both the oral and rectal route was recommended.

Treatment of salicylate poisonings is based on methods that have been used over the years. Forced alkaline diuresis has been one of the most popular treatments, but alkalinization alone is considered to be safer and equally successful [1], which suggests that forced diuresis is more effective theoretically than in reality. In addition, multiple-dose activated charcoal has been proposed to eliminate salicylates more effectively. Enteric-coated aspirin is more slowly absorbed and clinical symptoms of toxicity develop with a longer delay than following ingestion of regular aspirin [15]. In addition, enteric-coated tablets may accumulate in the stomach so that particular efforts should be paid to gastric emptying.

PARACETAMOL

Paracetamol (acetaminophen) is nowadays the most popular minor analgesic worldwide [16]. Acute poisonings due to paracetamol are extremely frequent and even though this drug has a very good level of safety at therapeutic doses, the hepatotoxicity of overdoses can lead to death, for example over 100 deaths a year in the United Kingdom [17,18]. Hawton [19] interviewed 80 patients with a history of suicidal paracetamol ingestion to identify the reason why they chose paracetamol to attempt suicide. One third chose paracetamol because they were aware of its potential toxicity even though less than 50% knew it was hepatotoxic. Approximately one half used paracetamol for therapeutic purposes. Interestingly, more than one half expected that CNS disorders would develop much more rapidly. This author [19] suggested that a better knowledge of paracetamol toxicity is unlikely to deter candidates from suicidal attempts and that improved packaging might be a safer alternative to prevent self-poisonings.

Paracetamol hepatotoxicity

Although nausea and vomiting may be the early signs of paracetamol poisoning, hepatotoxicity is the major feature as consciousness is usually unimpaired [16]. Hepatic tenderness may appear after 12 hours and hepatic necrosis becomes apparent in the few days after ingestion. Clinically and biologically, paracetamol-induced hepatotoxicity bears no specificities. The serum levels of the hepatic enzymes aspartate and alanine transaminases and lactate dehydrogenase increase dramatically and the increases reflect the degree of histological necrosis. Reduction in clotting factors, hypoglycemia, clinical features of encephalopathy (e.g. confusion, drowsiness, cerebral edema) are associated with severe hepatic injury. Renal failure is noted in approximately 2% of patients, an incidence similar to that associated with other causes of liver failure [16].

The biochemical basis of paracetamol hepatotoxicity was established in the 1970s: the oxidation of paracetamol ultimately leads to the reactive intermediate N-acetyl-para-benzoquinoneimine (NAPQI) which is rapidly metabolized to non toxic glutathione-dependent conjugates. When paracetamol is taken in toxic doses, hepatic glutathione becomes depleted and NAPQI can cause acute centrilobular hepatic necrosis due to direct cell damage [16].

A major recent concern is to determine the hepatotoxic dose of paracetamol as the liver is by far the main target organ of paracetamol toxicity. Hepatic injury has been reported following the ingestion of widely varying doses, for example from 2.5 g [20] to over 10–15 g [21].

Risk factors may significantly contribute to paracetamol toxicity and therefore account for these discrepancies. Whitcomb [22] retrospectively studied 126,770 inpatients from Pittsburgh hospitals between January 1987 and July 1993, for a correlation between paracetamol use, fasting, alcohol intake, and liver toxicity (ALAT > 1000 U/l). With paracetamol doses between 4 and 10 g,

hepatotoxicity was found to be correlated to fasting and less clearly to alcohol intake. It was concluded that paracetamol-associated hepatotoxicity is enhanced following the ingestion of 4 g in alcoholics, and/or in patients with underlying pathological conditions associated with fasting. Chronic alcohol intake has indeed been shown to be associated with increased liver damage due to paracetamol. Bray et al. [23] reported that survival was lowered by 33% in those patients with paracetamol overdose who drank above the Royal College of Physicians' recommended guidelines of 21 units per week for males and 14 for females. Interestingly, nephrotoxicity related to chronic alcohol intake was suggested to be the causative factor and the administration of N-acetylcysteine to chronic alcoholics was recommended even following a modest paracetamol dose. On the other hand, ethanol was suggested to exert a protective effect by reducing the formation of paracetamol hepatotoxic metabolites, but the clinical value of early experimental findings has not been tested [16]. Long-term anticonvulsant therapy was also reported to worsen paracetamol-induced fulminant hepatic failure [18,23]. Acidosis and severe coma were more frequent, as well as paracetamol-associated nephrotoxicity. Patients with a low-protein diet or vitamin-E deficiency have also been suggested to be at a higher risk of paracetamol hepatoxicity, whereas inhibitors of hepatic metabolism, such as piperonyl butoxide or cimetidine, antioxidants, calcium antagonists and allopurinol, have been suggested to reduce this risk at least in laboratory animals [16]. Interestingly, Bonkowsky et al. [25] reported one case of paracetamol-induced hepatoxicity in a 67-year-old man with cardiopulmonary and renal insufficiency after a daily intake of 3–4 g paracetamol for 2–4 days. He had paracetamol blood levels up to 30 μg/ml upon hospitalisation despite discontinuation of paracetamol 3 days before admission. This case report suggests that cardiac and renal insufficiency, and the resulting hypoxia, can be associated with enhanced paracetamol hepatotoxicity. Hypothermia as well as hypoxia are indeed well recognized situations resulting in alterations of hepatic drug metabolism, and as would be expected, Block et al. [26] reported the uneventful ingestion of 30 g paracetamol in a patient with profound hypothermia (circa 19°C). Despite paracetamol blood levels of 943 μM/l upon admission, no signs of hepatic injury were noted. Pregnancy has been suggested to be another risk factor of paracetamol hepatoxicity. However, paracetamol has actually no known teratogenic effects in animals [16] and suicidal attempts in pregnant women did not evidence a major risk for severe poisoning [27,28].

Management of acute poisoning

The management of paracetamol poisoning has ben the matter of extensive studies in the recent past [16,28]. Induction of emesis or gastric lavage is generally recommended in patients with a recent (less than 4 hours) or apparently important ingestion. Activated charcoal is a simpler method to prevent paracetamol absorption by the gut, and studies in healthy volunteers showed it is as effective as gastric lavage or induced emesis.

Even though several antidotal therapies have been proposed in the past, such as cysteamine, dimercaprol and penicillamine, or more recently, for example cimetidine, treatment of paracetamol poisoning is largely based on the administration of N-acetylcysteine (NAC) [16,28] even though methionine could also be used to replenish hepatic glutathione stores. NAC, the precursor of glutathione, can indeed help replenish glutathione stores depleted because of the need for NAPQI neutralization. The multicenter study by Smilkstein et al. [29] showed that NAC administration totally prevented paracetamol hepatotoxicity when administered within 8 hours post-ingestion. No lethality was noted when NAC was administered within 16 hours, and a reduced risk of severe hepatotoxicity was noted when NAC was administered up to 48 hours post-ingestion.

One recent issue dealing with NAC regards the route of administration. Even though US authors [29] maintained that oral NAC is equally effective as intravenous NAC despite a longer hospital stay, Keays et al. [30] found intravenous NAC to be effective in paracetamol-induced fulminant liver failure. Unfortunately, no clinical trials compared the two routes of administration [16]. Oral NAC is simpler, cheaper, and can be started outside the hospital. It is rarely associated with severe adverse effects and poor digestive tolerance, resulting in vomiting and diarrhoea, is the main untoward feature. Intravenous NAC is more practical in unconscious or vomiting patients but anaphylactoid reactions with rash, urticaria, angioedema, bronchospasm, hypotension and/or tachycardia may occur in 2–10% of patients [16]. The delay in administering NAC is another critical issue. The results of studies by Smilkstein et al. [29] as well as Keays et al. [30] suggest that late administration of NAC (up to 24 hours) may still be effective; however, no clinical trials have so far addressed this issue and the efficacy of late NAC administration is as yet unproven [16].

Another major issue in the treatment of paracetamol acute poisonings is related to prognosis. The most important early indicator is the plasma paracetamol levels. Prescott et al. [31] determined a relation between paracetamol concentrations and the severity of hepatic necrosis, using a semi-logarithmic plot. Patients "above the treatment line" have a higher risk of developing liver failure and should be given NAC. It should be kept in mind, however, that paracetamol concentrations do not correlate closely with hepatic necrosis until 4-6 hours after ingestion. Other important indicators of hepatic necrosis include the prothrombin time (PTR) and serum liver enzyme levels. Harrison et al [32] performed serial measurements of prothrombin time in 150 patients with paracetamol-induced fulminant hepatic failure. 72 (48%) patients died. 34 of the 37 (92%) with a peak prothrombin time of ≥180 seconds and 39 of the 42 (93%) patients with a continuing rise in prothrombin time at day four post-ingestion, died. Beckett et al. [33] measured the plasma concentration of glutathione S-transferase B_1 ($GSTB_1$) subunits, a very sensitive marker of hepatoxicity, in 10 patients with severe paracetamol poisoning treated with intravenous NAC. Interestingly, $GSTB_1$ levels decreased after starting NAC and none of the patients developed significant liver damage, which further supports the

protective effects of the antidote and its lack of hepatotoxicity, suspected from results on isolated hepatocytes.

Despite the usual efficacy of NAC in the management of acute paracetamol poisoning, other therapeutic measures should be considered [16,28]. Rigorous hepatic intensive care is obviously essential. Hemodialysis and charcoal hemoperfusion were suggested to be effective, essentially at an early stage, but there is no firm clinical evidence to support this view.

Finally, liver transplantation has been a matter of growing interest as severe liver failure is still seen in a small but significant fraction of patients [28]. No firm conclusion has been reached regarding early prognostic indicators of paracetamol-induced fulminant hepatic failure. Patients with a more probable fatal outcome include those with acidosis and a continuing rise in prothrombin time on day 4, and have therefore been suggested to be more likely to benefit from liver transplantation [17], as delay increases the risk of cerebral edema, hypotension, hemorrhage and renal failure, and decreases the likelihood of survival following transplantation.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Despite the widespread prescription of non-steroidal anti-inflammatory drugs (NSAID), acute poisonings are infrequent and very few reports are available in the literature [34–36]. As only isolated cases have been reported, it is difficult to draw a precise clinical picture of acute poisonings associated with a given compound, and the range of toxicity is also ill-established [35,36]. Typical signs and symptoms include nausea, vomiting, headache, drowsiness, blurred vision and dizziness. Seizures have been seldom documented. That acute poisonings with NSAIDs can be severe was exemplified by a recent case report [37]. A 44-year-old man ingested 72 g of ibuprofen. He developed recurrent emesis, metabolic acidosis, renal failure, hyperkalemia and rhabdomyolysis, but recovered uneventfully after supportive treatment.

Treatment is largely supportive. Activated charcoal has been shown to decrease the gastrointestinal absorption of various NSAIDs in human volunteers but it is unknown to what extent activated charcoal is effective in acute poisonings [36]. Forced diuresis, hemodialysis and hemoperfusion are unlikely to be of value with most NSAIDs because they are highly protein-bound.

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14. Anti-allergic drugs and antihistamines

When a clinician is confronted with a patient who has been exposed to a potentially toxic quantity of an antihistamine, it will be valuable to determine which chemical class of antihistamine was involved. The importance of establishing the identity of the ingested antihistamine has increased with the recognition of potentially life-threatening cardiac toxicity with relatively small exposures to terfenadine. This identification can often be accomplished by taking a good history, but may on occasion be established by performing a physical examination and identifying the class of antihistamine by recognizing a specific pattern of toxicity.

Antihistamines are available worldwide and many do not require a prescription. They are commonly used to provide symptomatic relief of cold and allergy symptoms. Several of the antihistamines with potent central nervous system depressant and anticholinergic properties are available as nonprescription sleep aids. At present, antagonists or antihistaminergic chemicals for three different histamine modulated receptor sites have been identified. This discussion will focus on toxicity, diagnosis and treatment of patients who have had an excessive exposure to H_1 or H_2 antagonists. The H_3 receptor antagonists which do not have a therapeutic use will not be addressed.

H_1 HISTAMINE RECEPTOR ANTAGONISTS

All of the histamine (H_1) antagonists are reversible, competitive inhibitors of histamine. Terfenadine has a distinct advantage in that it binds much more selectively to peripheral H_1 receptors and has a much more limited binding affinity to the cholinergic, α and β adrenergic receptor sites than do the other antihistamines. This has made this group of antihistamines extremely popular because at therapeutic doses their specificity for the peripheral histamine receptor site eliminates many side effects, including central nervous system (CNS) depression, blurred vision, dry mouth and tachycardia. Terfenadine and astemizole are postulated to cause less CNS depression than other H_1 antihistamines because they do not avidly partition across the blood brain barrier into the brain [1].

Alkylamines	
Brompheniramine	Chlorpheniramine
Dexbrompheniramine	Dexchlorpheniramine
Dimethindene	Pheniramine
Pyrrobutamine	Triprolidine
Ethylenediamines	
Antazoline	Methapyrilene
Phenyldiamine	Pyrilamine
Tripelennamine	
Piperazines	
Buclizine	Chlorcyclizine
Cyclizine	Meclizine
Hydroxyzine	
Ethanolamines	
Bromodiphenhydramine	Carbinoxamine
Clemastine	Dimenhydrinate
Diphenylhydramine	Diphenylpyraline
Doxylamine	Phenyltoloxamine
Phenothiazines	
Methdilazine	Promethazine
Trimeprazine	
Miscellaneous	
Astemizole	Azatadine
Cyproheptadine	Phenindamine
Terfenadine	

Table 14.1. *Major classes of H_1 antihistamines*

Many of the H_1 receptor antihistamines are substituted ethylamine structures with a tertiary amino group linked by a two- to three-carbon chain with two aromatic groups [2]. This differs from histamine by the absence of a primary amino group and the presence of a single aromatic moiety. There are six major classes of antihistamines (H_1 histamine receptor antagonists). These are the ethylenediamine and ethanolamine derivatives, the alkylamines, the phenothiazine and piperazine derivatives, and the peripherally selective H_1 antagonists astemizole and terfenadine (see Table 14.1).

Diagnostic findings

Acute toxicity. Following the exposure to an excessive amount of all of the H_1 receptor antagonists except terfenadine and astemizole, the adult patient will present with CNS depression and excessive anticholinergic symptoms. In

a review of 136 patients with diphenhydramine overdose, an impairment in consciousness was the most common finding and a catatonic stupor was considered as a highly specific finding for those who ingested diphenylhydramine [3]. Several reports suggest that young children manifest CNS stimulation and excessive anticholinergic symptoms.

Mydriasis is one of the most common anticholinergic symptoms observed with overdose. Many patients will have dilated pupils following therapeutic doses of antihistamines with potent anticholinergic effects and will complain of blurred vision and/or diplopia. Both vertical and horizontal nystagmus has been reported with diphenhydramine [4]. Other CNS effects may include seizures, hallucinations, dystonic reactions and toxic psychoses [5–8]. A severe anxiety reaction has been reported after the first therapeutic dose of terfenadine [9]. This is considered to be an adverse drug reaction and not a symptom of an acute overdose. Sedation without other anticholinergic effects has been reported with terfenadine and astemizole.

A sinus tachycardia is a consistent finding in any exposure that has anticholinergic effects. The absence of a tachycardia should lead to suspicion that exposure to an anticholinergic substance has not occurred, or the patient has been exposed to another toxin capable of preventing the development of a tachycardia. Hypotension or hypertension have been reported to occur with tachycardia and probably relate to the patient's age, state of hydration and vascular tone.

Following large diphenhydramine overdoses, prolonged QT intervals and QRS complexes may be observed [10,11]. Overexposure to terfenadine has resulted in hypotension, palpitations and syncope. Torsades de pointes and other life-threatening ventricular arrhythmias have been reported in overdoses of terfenadine [12,13]. These dysrhythmias have also been reported in patients with significant hepatic dysfunction receiving therapeutic doses of terfenadine, and even in patients with normal hepatic function who are concurrently receiving erythromycin, troleandomycin or ketoconazole. Doses as low as 360 mg of terfenadine may cause QT interval prolongation and ventricular dysrhythmias in normal individuals without identifiable risk factors [14].

The anticholinergic symptoms commonly seen in both adults and children can be observed at all hollow viscous organs. All mucous membranes and skin surfaces will appear dry. The skin may appear flushed and warm and even if the patient is agitated there will be a notable absence of sweat. Agitation concomitant with the inability to sweat usually results in hyperthermia that can be correlated with the extent of agitation, the ambient temperature and humidity, and the length of time during which the patient has been unable to dissipate heat. Muscle breakdown can occur with extreme agitation. Rhabdomyolysis has been reported in seven patients with doxylamine overdoses who did not have any mechanical reasons such as seizures, shock or crush injuries to explain the etiology of the rhabdomyolysis [15]. Urinary retention has been associated with all of the antihistamines with anticholinergic properties [5]. Gastrointestinal symptoms include nausea, vomiting, diarrhea and constipation and vary depending upon the specific medication [16].

Chronic toxicity. Chronic toxicity from H_1 antihistamines is uncommon but can be life-threatening. Agranulocytosis has been reported with both chlorpheniramine and brompheniramine [17,18]. A single case of cholestatic jaundice has been reported after prolonged treatment with 12 mg per day of cyproheptadine [19]. A second case of hepatitis with jaundice has been reported following 17 months of therapy with terfenadine [20]. No mechanism of toxicity has been defined for these cases of proposed hepatotoxicity. Patients with chronic obstructive pulmonary disease or asthma may have a worsening of their disease due to an inspiration of bronchial secretions [21].

Differential diagnosis. The list of substances that can manifest similar signs and symptoms to the toxic effects of antihistamines is extensive. The differential diagnosis becomes broader and even more complex if the antihistamine is combined with decongestants and/or analgesics.

Those agents most commonly responsible for anticholinergic syndromes may include many of the cyclic antidepressants, phenothiazines, antispasmodics and the anticholinergic drugs that are used to treat or prevent extrapyramidal symptoms associated with phenothiazine or butyrophenone therapy.

Plants containing the belladonna alkaloids such as jimson weed (*Datura stramonium*), angel's trumpet (*Solandra* spp.) and nightshade (*Atropa belladona*) will also present with anticholinergic symptoms if ingested. Several species of Amanita mushrooms (*A. muscaria, A. gemmata, A. pantherina*) that contain ibotenic acid and muscimol will also produce anticholinergic findings if ingested.

Many of the therapeutic strategies that have been developed to stabilize and treat antihistamine toxicity are based upon the knowledge that the identity of a specific toxin or medication may not be available at the time patient care has to be provided.

Treatment. The initial intervention in any overdosed patient is to establish an airway and ensure oxygenation and ventilation. Resuscitative measures should be initiated promptly if they are required. The vital signs should be checked and recorded frequently during the first few hours.

On initial presentation the patient who is likely to develop a severe complication may not be easily distinguished from the patient who will have a totally benign course. Therefore, the patient should be placed on a cardiac monitor, have intravenous access established and blood obtained for routine laboratory studies. The distinction can often be made with serial assessments of vital signs and mental status. Particular attention should be given to the patient with a rising temperature or pulse rate as these findings are often prognostic of worsening toxicity. Typically, the patient who is going to require more than supportive care will have unstable vital signs or a mental status that fails to improve or deteriorates after several hours. This potential for a precipitous clinical deterioration necessitates that the patient be triaged to a critical care environment where life-support is immediately available if stabilization of the airway, cardiovascular or thermoregulatory systems becomes necessary.

The vast majority of patients with H_1 antihistamine ingestions will present with CNS depression which can be managed with supportive care and a dose

of activated charcoal. Symptoms of toxicity will usually resolve within 8 to 16 hours. The most serious complications include life-threatening ventricular dysrhythmias, seizures, hypotension or hyperthermia.

(1) *Life-threatening complications.* In all patients with an altered consciousness, after initial laboratory studies have been drawn, a bolus of intravenous dextrose (100 ml of 50% adults, or 1 g/kg of 25% solution for children) should be administered to exclude the possibility of hypoglycemia. Monitoring of the patient's blood glucose and electrolytes should be performed until the patient's mental status returns to normal.

If the patient is hypotensive, normal saline or lactated ringers intravenous fluids should be administered and the patient should be placed in the Trendelenburg position. If the desired increase in blood pressure is not attained, dopamine (2–10 μg/kg/min) or levarterenol (0.1–0.2 μg/kg/min) may be titrated to achieve an acceptable blood pressure. Cardiogenic shock and myocardial depression that resulted from a 10 g ingestion of pyrilamine maleate was reversed with an intra-aortic-balloon counterpulsation device [22].

Extreme agitation, hallucinations, and psychosis should be treated with the administration of either physostigmine or diazepam. If the patient has characteristic anticholinergic symptoms, a narrow QRS complex and no history of exposure to a cyclic antidepressant, physostigmine may be a safe and effective antidote. If the history is uncertain, or the ECG manifests a wide complex or if the physician is uncertain if physostigmine is safe to employ, diazepam 5–10 mg intravenously (adults) or 0.25 mg/kg to a maximum of 5 mg (children less than 5 years) will be an equally efficacious and safe alternative. The diazepam dose may be repeated as necessary until the patient's agitation is controlled and he/she is resting comfortably.

The dosing and precautions that must be used in the administration of physostigmine will be discussed later in this chapter. Vital signs must be frequently assessed during the administration of either intravenous diazepam or physostigmine. The presence of agitation should heighten the awareness that hyperthermia may be present or may develop. If the patient's temperature has reached 40.5°C or the temperature is rising rapidly the patient should be promptly cooled in an ice bath or with cold water mist and fan.

If the patient develops a seizure, diazepam 5–10 mg intravenously (adults) or 0.25 mg/kg to a maximum of 5 mg (children less than 5 years), and/or phenobarbital 10–15 mg/kg may be required. If the seizures are refractory to the diazepam and phenobarbital, general anesthesia with thiopental or halothane and paralysis with a neuromuscular blocking agent may be necessary.

Ventricular dysrhythmias may respond to the administration of standard doses of lidocaine or bretylium. The class Ia and class IC antiarrhythmic agents should be avoided as they may further decrease intraventricular conduction. If an intraventricular conduction delay (prolonged QRS complex) is noted on the electrocardiogram sodium bicarbonate (1–2 mEq/kg) should be administered intravenously. If sodium bicarbonate is administered as a therapeutic gesture for the intraventricular conduction delay, the patient's arterial blood pH should

be maintained in a range between 7.40–7.50. During alkalinization the patient's electrolytes and renal function must be closely followed with repetitive laboratory determinations.

Torsade de pointes ("twisting of the points"), which is a variation of ventricular tachycardia with polymorphic QRS complexes, is now recognized as a major toxicity with terfenadine in overdose, or following standard dosing in patients with hepatic dysfunction or in patients concurrently receiving erythromycin or ketoconazole. If torsade de pointes is complicated by hypotension, myocardial ischemia, or congestive heart failure cardioversion should be the initial treatment. The success rate for cardioversion of drug induced arrhythmias is limited due to the persistence of the effects of the etiologic toxin and additional interventions will usually be required. Magnesium sulfate 2–6 g (16–48 mEq) should be administered as a slow intravenous bolus. When magnesium sulfate is administered, the patient should be carefully monitored for changes in blood pressure, rhythm and reflexes. If the ventricular arrhythmia remains unresponsive, overdrive pacing may be necessary.

If the patient with clearly defined anticholinergic symptoms develops a narrow QRS complex supraventricular tachycardia with either hemodynamic instability or ischemic chest pain, the patient should be given oxygen, and physostigmine (1–2 mg for adults, 0.5 mg for children) may be cautiously administered intravenously over two to three minutes. Most patients who develop a supraventricular tachycardia from an antihistamine exposure will not require pharmacologic interventions.

(2) *Gastrointestinal decontamination.* The patient who has minimal CNS depression but retains a good gag reflex and can safely take liquids by mouth, should receive a slurry of 1 g/kg of body weight of activated charcoal mixed in water to drink. A cathartic such as magnesium or sodium sulfate 30 g (adults) or 250 mg/kg (children) or sorbitol 1.5 g/kg of body weight can be added to the water slurry.

The patient with significant CNS depression who lacks a gag reflex and is unable to protect his/her airway should have endotracheal intubation performed prior to proceeding with gastric lavage using a large bore orogastric tube. In those patients with intermediate clinical states who are uncooperative without a gag reflex, deterioration should be expected and sedation should be administered to allow endotracheal intubation and gastric lavage. Activated charcoal (1 g/kg of body weight) in a water slurry should be instilled through the lavage tube with a cathartic such as magnesium or sodium sulfate [30 g (adults) or 250 mg/kg (children)] or sorbitol (1.5 g/kg of body weight).

Emesis with syrup of ipecac is reserved solely for the patient who has been witnessed to have "just" ingested the antihistamine and can be treated immediately. If more than 1 hour has elapsed since the ingestion, ipecac may not be safe because the patient's CNS and/or cardiovascular function may deteriorate precipitously prior to emesis. In the emergency department the administration of the syrup of ipecac may delay the administration of activated charcoal which may be an essential therapeutic intervention for this overdose.

(3) *Reversal of anticholinergic symptoms*. Physostigmine can be an extremely effective antidote for anticholinergic toxicity. For physostigmine to be used safely the patient should have both central and peripheral anticholinergic effects, a narrow QRS complex on ECG, a narrow QRS complex on the currently obtained monitor strip and no history of exposure to other toxins that may cause intraventricular conduction delays such as cocaine, quinidine, procainamide, disopyramide, the cyclic antidepressants, mesoridazine, and thioridazine.

If the patient has the characteristic symptoms of anticholinergic toxicity (i.e. dilated pupils, tachycardia, dry skin, diminished bowel sounds, urinary retention, etc.), and CNS depression, severe agitation, hallucinations or a consequential supraventricular tachycardia, a trial dose of physostigmine may be administered. It must always be determined that the benefits of physostigmine outweigh the potential risks prior to use. The physician should be familiar with the potential life-threatening complications associated with the use of physostigmine. The patient should be placed on a cardiac monitor and have a secure intravenous access site available. Physostigmine (2 mg in adults, 0.5 mg in children) should be administered by slow intravenous push. This dose may be repeated at 5–10 minute intervals if the reversal of anticholinergic symptoms does not occur and cholinergic symptoms do not appear. If improvement occurs it may be necessary to readminister the physostigmine at 30–60 minute intervals. With each readministration the minimum dose to reverse anticholinergic toxicity must be determined. A dose of intravenous atropine equal to one-half of the dose in mg of physostigmine should be available at the patient's bedside if cholinergic toxicity occurs. Cholinergic toxicity from physostigmine may include bronchospasm, bradycardia, hypersalivation, diaphoresis, and incontinence of urine and stool.

Toxicology laboratory testing. There appears to be little justification for obtaining either qualitative testing or quantitative screening of the blood or urine for antihistamines. Most laboratories are not capable of testing for H_1 antihistamines. There does not appear to be a clear distinction between therapeutic and toxic blood levels.

All adult intentional ingestions and massive pediatric ingestions should have blood obtained at 4 hours or as soon thereafter as possible for acetaminophen (paracetamol) and salicylate determinations. Many of the cough and cold preparations combine H_1 antihistamines and analgesics. The results from these two determinations should be available to the clinician within 4 hours so that if needed, N-acetylcysteine (acetaminophen) or alkalinization of the urine (salicylates) can be started promptly.

H_2 HISTAMINE RECEPTOR ANTAGONISTS

The H_2 receptor antagonists became available shortly after the characterization of the H_2 receptor [23]. They are presently in widespread use for the treatment of peptic and duodenal ulcer diseases, and acid hypersecretory states

including Zollinger–Ellison syndrome. Less common uses include systemic mastocytosis and multiple endocrine adenomas.

Cimetidine is the prototype H_2 receptor antagonist. Cimetidine is rapidly and completely absorbed following oral administration. Cimetidine has a volume of distribution of approximately 2 l/kg with 13–25% protein binding [24]. Seventy percent of cimetidine is eliminated unchanged in the urine, 15% is metabolized by the liver, and 10% is found unchanged in the stool [25]. The elimination half-life in patients with normal renal function is approximately 2 hours [24]. Cimetidine is responsible for numerous drug–drug interactions because it can inhibit cytochrome P-450 mixed function oxidase activity, and can reduce hepatic blood flow. Cimetidine has been implicated in causing significant drug interactions with beta-adrenergic antagonists, carbamazepine, lidocaine, phenytoin, procainamide, quinidine, salicylates, theophylline, verapamil, and warfarin [26]. Interestingly, metabolic interactions have similarly been shown to occur with the pesticide carbaryl [27]. All of the other available H_2 receptor antagonists, particularly ranitidine [28], have been shown not to inhibit the cytochrome P-450 mixed function oxidase system.

Acute toxic effects. Acute toxic effects appear to be extremely rare following large (20 g) oral ingestions of cimetidine [29]. Nelson [30] reported one patient however who, following a 12 g ingestion, developed tachycardia, dilated-sluggishly reactive pupils, and slurred speech.

Bradycardia, hypotension, and cardiac arrest have followed rapid intravenous administration in seriously ill patients [30].

Treatment. The treatment of an acute oral ingestion of an H_2 receptor antagonist overdose should include the administration of activated charcoal along with rigorous assessment of the patient to exclude a coingestant. Emesis with syrup of ipecac, gastric lavage, diuresis, hemodialysis, or charcoal-hemoperfusion are not indicated and have not been shown to be beneficial for this overdose. Plasma drug concentrations for the H_2 receptor antagonists are not routinely performed by most clinical laboratories and drug concentrations have not been shown to correlate with toxic effects [25].

The patient who manifests cardiac toxicity following the intravenous administration of cimetidine should be treated with standard resuscitative therapies keeping in mind that cimetidine may reduce the metabolism of many of the antidysrythmic medications.

Chronic cimetidine toxicity appears to occur most commonly in the elderly and in those patients with impaired renal function. The symptoms most commonly associated with chronic toxicity include confusion, somnolence, lethargy, visual hallucinations and slurred speech.

CONCLUSION

The popularity and availability of antihistamines make them readily accessible for overdose in both adults and children. Fortunately, even the vast

majority of patients who significantly exceed the recommended dose or dosing schedule will have excellent outcomes with no expected sequellae if they receive supportive care, activated charcoal and continuous assessment of their vital signs, electrocardiogram and mental status during the critical phase. If the clinician is familiar with the more severe sequellae of antihistamine overdoses, early and appropriate interventions will reduce both morbidity and mortality from these exposures.

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15. Antimicrobials

INTRODUCTION

In sharp contrast to side effects, acute poisonings with antimicrobials are rare and usually mild.

ANTITUBERCULOSIS AGENTS

Ethambutol

Ethambutol overdoses often involve combination with other antituberculosis agents such as isoniazid or rifampin. In such cases ethambutol toxicity is augmented. The most prominent toxic manifestation is neuritis, but different central and peripheral neurologic involvement have also been reported. Optic neuritis of two different types has been identified [1,2], one involving the central and the other the peripheral fibers of the optic nerve. While the first type results in considerable visual impairment, the latter usually does not affect visual acuity. The doses inducing these changes are in excess of 15 mg/kg. Doses of 35 mg/kg or greater have caused optic neuritis in more than 15% of treated patients [1,2]. One case of optic neuritis has been reported following an acute overdose of 10 g [3].

Acute overdose has been reported to be associated with mental confusion, visual hallucinations, nausea and abdominal pain [3]. Long-term intake of 1200–1400 mg/day has resulted in peripheral neuropathy [4]. 20 g have been taken acutely without liver or eye injury [5] and can be considered as the maximum tolerated dose.

Since no specific antidote is available, treatment is symptomatic and supportive. Gastric emptying either by emesis or gastric lavage is only indicated in substantial recent ingestions. Emesis is most effective within a time period of 30 minutes post-ingestion. Activated charcoal is recommended according to general rules of administration.

Isoniazid

Clinical effects. One case of visual disturbances following the ingestion of 3.6 g has been described [6]. Hypotension and tachycardia have been considered to result from acute isoniazid overdose. Respiratory depression is frequently observed as a complication of seizures. When seizures are absent or between attacks, Kussmaul-type respiration may be noted [7]. The first symptoms of overdosage are: slurred speech, dizziness, lethargy, disorientation, and ataxia. These are followed by stupor, areflexia or hyperreflexia, and a positive Babinski sign. Finally, seizures and coma occur generally within one hour post-ingestion with a range of 30 minutes to 5 hours [8–11].

Nausea and vomiting frequently precede the onset of seizures. Several cases of mild hepatic dysfunction after acute overdose have been reported [6,12–14]. Jaundice is thought to be encountered in about 0.6% of treated patients. Albuminuria and oliguria leading to anuria have been observed. Acute exposure has been accompanied by ketonuria, hyperglycemia and hyperkalemia [7]. Severe metabolic acidosis with marked anion gap frequently unresponsive to intravenous sodium bicarbonate has been noted [9,15].

Treatment. Gastric emptying by either emesis or lavage is indicated. The time lag until the occurrence of seizures after ingestion (usually 1 to 3 hours, but sometimes 30 to 60 minutes) has to be taken into account before inducing emesis. Generally, gastric lavage is indicated soon after isoniazid ingestion or in comatose patients who are at risk of convulsing. Activated charcoal failed to reduce the bioavailability and half-life of isoniazid in volunteers one hour after a therapeutic dose [16]. For seizure control, anticonvulsive drugs such as diazepam should be administered. Repeatedly, pyridoxine was used successfully to prevent or treat vital complications such as seizures, coma and acidosis [9,17–20]. For this purpose, an intravenous dose equivalent to the amount of isoniazid ingested is recommended. Thus, initially, up to 5 g over 30 to 60 minutes are given. If necessary, the remaining dose may be given by intravenous drip over the next one to two hours [9]. Unknown ingestions should be treated with a single dose of 5 g pyridoxine which may be repeated within 15 minutes if there is no response. Normally, acidosis resolves after the administration of pyridoxine and diazepam. However, severe acidosis should be corrected first to a pH of at least 7.2 [20]. Hypotension is usually controlled by intravenous fluids and, if necessary, by the administration of dopamine or norepinephrine. Among extracorporeal elimination procedures, hemodialysis has been employed in a few instances, but with limited success [13].

Rifampin

Clinical effects. The most striking phenomenon induced by rifampin overdose is the "Red-Orange Person Syndrome" which is characterized by red discoloration of the skin, urine, feces, sclera, and sweat [21,22]. A review of the literature [22] revealed 29 patients, 9 of whom ingested rifampin intentionally

and with 20 children who were accidentally given an overdose. The ingested doses ranged from 9 to 60 g. Three deaths were recorded. The author stated that a dose of 14 g rifampin is probably associated with cardiopulmonary arrest.

There are several reports of facial edema. The doses amounted to 100 mg/kg in children and 12 g in adults [21,23,24]. One report considered pulmonary edema as the cause of death following rifampin overdose [25].

Nausea and vomiting are frequently reported. Hepatic injury, a typical complication of rifampicin therapy was also reported following acute overdose. Thrombocytopenia and purpura may occur during therapy but eosinophilia resulted from a suicidal overdose [26].

Acute toxicity has been observed in children receiving 500 mg/kg [24]. Two patients died after the ingestion of 14 and 60 g.

Treatment. Gastric emptying either by emesis or lavage is indicated after massive overdose. Activated charcoal is recommended. Due to the enterohepatic circulation of rifampin, repeated charcoal administration may be beneficial in enhancing the total body clearance of the drug. Altogether, clinical experience with rifampin overdose is limited.

SULFONAMIDES

The majority of sulfonamide-induced toxic effects are hypersensitivity reactions involving nearly every organ system and with variable clinical features. Nevertheless, there seems to be a relationship between the dose and incidence of adverse reactions with slight differences between short-acting and long-acting derivatives.

The ingestion of 8 g sulfamethoxazole and 1.6 g trimethoprim resulted in renal failure in an elderly man [27].

PENICILLINS

The most frequent adverse effects of penicillins are hypersensitivity reactions occurring in 1–10% of treated patients. The incidence of anaphylactic shock is 1 to 5 per 10 000 with resulting death in a high percentage. While severe oral intoxication is unlikely, intravenous injection of large doses may be linked to neurotoxicity. Large intravenous doses may evoke drowsiness, myoclonus, seizures and coma [28,29]. Impaired renal function is an aggravating factor [30]. Neurotoxicity may be partly due to the procaine moiety of certain slow-release preparations and possible micro-embolism.

A 3-year-old boy who ingested 574 mg/kg amoxicillin developed acute oliguric renal failure [31]. On the other hand, 80% of children who ingested 250 mg/kg amoxicillin remained asymptomatic [32]. Large doses of sodium or potassium penicillin G or carbenicillin disodium may cause electrolyte imbalance.

Gastric emptying by either emesis or lavage is indicated after massive overdose. The highest efficacy of these measures is considered to be within 30 minutes post-ingestion. Activated charcoal is highly effective [33].

CEPHALOSPORINS

Generally, the toxicology of cephalosporins resembles that of the penicillins. Nevertheless, there are some specific aspects which will be briefly outlined. Seizures, syncopal episode and encephalopathy are the most significant among the neurologic symptoms described. Cephalosporin derivatives responsible for neurotoxic manifestations were moxalactam [34], cefonicid [35] and cephazolin [36,37]. A dose of 1 g moxalactam caused seizures in a 91-year-old man with impaired renal function [34].

Gastric emptying by either emesis or lavage is indicated after massive overdose. The highest efficacy of these measures is considered to be within 30 minutes post-ingestion. Activated charcoal is probably effective.

ERYTHROMYCIN

Erythromycin is one of the safest antibiotics, causing poisoning only very rarely. There are only a few case reports of acute overdose in the literature and clinical experience largely refers to untoward effects during therapy.

One case of pancreatitis after acute overdose has been reported [38]. Approximately three hours post-ingestion the patient developed nausea, vomiting and severe epigastric pain. In another report, a 12-year-old girl who had ingested 5 g erythromycin, developed acute pancreatitis [39]. There is no specific treatment known.

CHLORAMPHENICOL

Optic neuritis has been reported in patients undergoing long-term therapy with chloramphenicol, and even optic atrophy with blindness has occurred. Nevertheless, optic disturbances are often reversible after early withdrawal of the drug [40].

Heart failure with bilateral ventricular dilation has been reported in a patient who died during treatment with chloramphenicol [41]. Reportedly, cardiovascular collapse has occurred in a young anephric patient receiving therapeutic doses [42]. Chloramphenicol toxicity has been considered the cause of left ventricular cardiac dysfunction which alleviated after withdrawal of the drug [43]. On the other hand, no serious cardiac effects have been observed in 231 patients receiving chloramphenicol [44].

Cardiovascular collapse and respiratory failure have been described in neonates and premature infants given high doses of chloramphenicol (50 to 100 mg/kg), and in critically ill infants with hepatic disease. The so-called "gray baby syndrome" is characterized by abdominal distention, vomiting, pallor and cyanosis, in addition to cardiovascular disturbances often resulting in death [45]. Similar syndromes have been encountered in adult patients with overdose and in patients with hepatic disease.

Among gastrointestinal disturbances, nausea, vomiting and diarrhea are to be mentioned. Furthermore, glossitis, stomatitis and enterocolitis have occurred. Rare cases of chloramphenicol-induced hepatotoxicity resulting in jaundice have been reported. Metabolic acidosis relatively resistant to bicarbonate may occur [46].

Bone marrow suppression of two different kinds associated with chloramphenicol is known: one is a dose-related, reversible form characterized by anemia, reticulocytopenia, leukopenia and thrombocytopenia in variable combinations. These toxic effects are induced by daily doses above 4 g and resolve after discontinuation of the drug. The second type is a dose-independent and irreversible aplastic anemia with a rare incidence but high mortality rate.

A 5-week-old child died after receiving 1100 mg and a 70-year-old patient died after taking approximately 400 mg/kg. On the other hand, a 26-year-old female recovered after receiving 21 g intravenously [47]. A neonate developed severe toxicity including the gray baby syndrome following inadvertent administration of 250 mg chloramphenicol/kg. She recovered after exchange transfusion [48].

Adequate emergency measures and intensive supportive therapy are required in severe cases with cardiorespiratory impairment. Gastric emptying by either emesis or gastric lavage is indicated as well as activated charcoal. In severe poisoning with high serum drug concentrations (>30 μg/ml), charcoal hemoperfusion may be considered. Massive overdose in neonates and infants may be treated by exchange transfusion although the efficacy of this technique is reportedly equivocal [49–51].

AMINOGLYCOSIDES

Poisoning with aminoglycosides is most frequently caused by inadvertent intravenous overdoses during treatment. Usually toxicity involves the kidneys [52–55] and the ears [52], but reports of acute overdose are rare. Aminoglycoside overdose in patients with normal renal function is usually well tolerated [56].

TETRACYCLINES

Due to their low toxicity, tetracyclines are unlikely to cause severe manifestations following acute overdose. Oesophageal ulceration and esophagitis have been reported following tetracycline or doxycycline ingestion [57,58]. A fatal case has been described which was presumably caused by a tetracycline-induced oesophago-atrial fistula [59]. Hepatic injury and gastro-intestinal side-effects have been described in the therapeutic setting. Nephrotoxicity, characterized as a Fanconi-like syndrome, due to the administration of outdated tetracycline preparations has been described [60], but is actually rare.

No specific measures are recommended for treating acute tetracycline overdose. Interestingly, activated charcoal was found to adsorb tetracyclines very effectively.

DAPSONE

Due to pronounced effects on erythrocytes and the central nervous system, the incidence of dapsone poisonings is high. The pathophysiological mechanism is based on an interaction with the hemoglobin molecule leading to the formation of methemoglobin and sulfhemoglobin. In addition, hemolysis occurs. The resulting impairment of oxygen exchange is responsible for the neurologic effects and cyanosis.

Tachycardia and, both hypertension and hypotension, have been reported [61–64]. Exertional dyspnea and hyperventilation with moderate impairment of oxygenation have also been noted [63]. CNS stimulation is manifested by giddiness, dizziness, confusion, aggressivity, agitation and hallucinations. Headaches are quite common and even one case of dapsone overdose with coma has been reported [62,65]. Three cases of motor neuropathy have been described [66]. Other signs and symptoms of dapsone overdose include nausea, vomiting and severe abdominal pain [67], laboratory evidence of hepatic involvement, hematuria [65], acidosis or alkalosis [63,68]

Methemoglobinemia and related cyanosis are almost invariably linked to dapsone poisoning. They may last for 3 to 10 days. The ingested dose leading to methemoglobinemia reportedly ranged from 100 mg in an 18-month-old child to 3 g in adults [62,63,68–70]. A 3.5-year-old girl suffered from persistent and recurrent methemoglobinemia which resolved within 2 weeks of admission, following the ingestion of an unknown amount of dapsone [71]. Sulfhemoglobinemia following an initial episode of methemoglobinemia was observed in a patient after ingesting 3 g dapsone. The onset of sulfhemoglobinemia was delayed to 4 days after dapsone ingestion and eventually followed by hemolytic anemia [62]. Not only dose-related hemolytic anemia is a common sign of dapsone toxicity, but also Heinz body hemolytic anemia is regularly observed [62–64,72,73]. The onset of hemolysis varies from 3 to 9 days post ingestion.

Gastric emptying by emesis or gastric lavage is indicated within 4 hours post-ingestion. Activated charcoal is effective to reduce gastrointestinal absorption and increase the elimination of dapsone and its metabolites. Repeat doses of oral charcoal were shown to be as effective as hemodialysis [64]. Methemoglobinemia is treated by administration of oxygen and methylene blue irrespective of the clinical appearance. Methylene blue is administered at a dose of 1 to 2 mg/kg intravenously over a few minutes every 4 hours as needed. Due to rebound methemoglobinemia, methylene blue treatment may be required for several days. Methemoglobin levels must be monitored repeatedly. Due to sulfhemoglobin formation, cyanosis may persist even though methemoglobin level has returned to normal. Methylene blue has no effect on sulfhemoglobinemia. Hemolysis parameters also need to be monitored particularly because of the hemolytic side effects of methylene blue on the one hand, and the delayed onset and long duration of dapsone-induced hemolysis on the other hand. Occasionally, blood transfusions are required. Extracorporeal elimina-

tion, namely hemodialysis and hemoperfusion, did not yield convincing results [61,63]. Exchange transfusion was successful in a 2-year-old child [73].

METRONIDAZOLE

Due to its low toxicity, metronidazole is not likely to cause acute poisoning. Doses up to 12 g have been ingested without significant signs of toxicity. Major neurotoxic effects, namely convulsions, have only been encountered with long-term treatment and appear to be dose-dependent in a cumulative sense. The ingestion of 1000 mg metronidazole has been reported to cause arm tremor and oculogyric crisis in a 33-year-old female patient [74] Metronidazole is supposed to cause disulfiram-like effects when combined with alcohol, but this has not yet been established by controlled studies. There are several anecdotal reports of combined metronidazole-alcohol abuse [75].

Gastric emptying within 3 hours is only indicated when massive doses (>10 g) have been ingested. Activated charcoal may be sufficiently effective in the majority of cases. Anticonvulsive and general supportive measures may be necessary in rare severe cases. Data on extracorporeal elimination procedures are inadequate and anyhow, their clinical need appears to be extremely unlikely.

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16. Anticancer drugs and immunomodulators

Cytostatics belong to a class of drugs with a narrow therapeutic index resulting in frequent and severe adverse effects. In the past, considerable efforts have been made to avoid or decrease significant toxicity, of which preventive measures [1,2] or optimal management [3] have been emphasized, but acute overdose may still occur. Adverse effects in health-care workers handling cytostatics are also of great concern.

OCCUPATIONAL TOXICITY OF ANTICANCER DRUGS

The exposure of health-care workers to cytostatic agents has been assessed in several studies. Transcutaneous uptake and inhalation are the suggested routes of exposure in hospital nurses or pharmacists handling cytostatics.

The possibility of acute local and systemic adverse effects associated with antineoplastic drug handling has indeed been suggested from case reports or small controlled studies. Overall, few reports of acute effects from work exposure are available, and most of them were described in handlers not using standard precautions. Accidental ingestion, inhalation of microparticles following aerosol, dermal and ocular exposure are the primary routes of occupational exposure while preparing and/or administering these agents.

Toxic effects

Ocular exposure to doxorubicin resulted in no reaction or rapidly resolving conjunctivitis in 13 of 15 cases [4]. Chronic inflammation and persistent photophobia were noted in the 2 remaining cases. Isolated and unconfirmed case reports have described the occurrence of neurological symptoms, hair loss and liver injury in 3 nurses after years of bleomycin, cyclophosphamide and vincristine handling [5]. Other reported symptoms include severe gastrointestinal disturbances following cutaneous exposure to carmustine or acute respiratory symptoms after preparing vincristine [6], facial flushing and dizziness

related to cisplatin or dacarbazine handling [7], nausea, vomiting, urticaria and headache with amsacrine [8], immediate hypersensitivity reactions and contact dermatitis with handling of various agent, for example azathioprine, bleomycin, cisplatin, cyclophosphamide, doxorubicin, fluorouracil, methotrexate and mitomycin C [6,9–12].

A recent report using data derived from a cross-sectional survey by questionnaire of nurses, nurse aides, pharmacists and pharmacy technicians showed the handling of antineoplastics was associated with a small but significant increase in symptoms when compared to controls [13]. A further analysis found that the single most important predictor of symptoms was skin contact during drug handling. However, the interpretation of data was limited by the volunteer-based sample and moderate participation rates.

Biomarkers of toxicity

The detection, quantification and surveillance of exposure to antineoplastic agents has been performed using physical examination, urine mutagenicity [14], evaluation of peripheral blood or marrow abnormalities [15], laboratory tests focusing on other target organs (liver and kidney), and biological monitoring of a specific agent or its metabolites in the urine or blood of hospital personnel [16].

Mutagenicity. Since the early 1980s, many mutagenic and cytogenetic studies have been performed in health-care workers exposed to antineoplastic drugs, mostly alkylating agents [14]. Results were often conflicting and a comparison between studies is difficult due to the different conditions of exposure. An increase in urine mutagenicity has been observed in nurses handling cytostatic drugs without sufficient precautions, while results obtained in nurses preparing cytostatics in a horizontal or vertical laminar-flow hood were negative [14,17]. Again the demonstration of increased sister chromatid exchanges or chromosomally aberrant lymphocytes in nurses has led to divergent results depending on the estimated quantitative exposure and the use of protective measures [17]. Bacterial mutagenicity test and sister chromatid exchange analysis cannot be considered as reliable indicators of exposure to cytostatic drugs, especially when safe handling conditions are applied as recommended [14,16,18,19]. Furthermore, it remains impossible to interpret a positive result accurately.

Extrapolation to the clinical setting is difficult and detrimental long-term health consequences of contact with cytotoxic drugs have not yet been clearly demonstrated. One study on cancer morbidity has found an increased relative risk for leukemia in nurses handling cytostatics, but these results were based on two cases only [20].

Analytical monitoring. Few investigations on the biological monitoring of workers exposed to cytostatic drugs have been performed. Early reports showed a minimal amount of cyclophosphamide in the urine of exposed health workers without protective clothing [21]. More recently, a highly sensitive

assay method was shown to detect very low levels of platinum [22], cyclophosphamide or ifosfamide [23, 24] in the urine of hospital personnel, and methotrexate in the urine of pharmaceutical plant workers [25]. The uptake was estimated to be far less than 0.01% of the handled dose, but all drugs were detected despite safety precautions during preparation of these drugs. These results further demonstrate that the handling of cytotoxic drugs may result in contamination of the environment. However, such a detection is only indicative of exposure. Furthermore, the threshold value for unacceptable concentrations in health workers has not yet been determined.

Pregnancy

The consequences of handling cytostatics drugs during pregnancy have been analyzed in few epidemiological studies. While two retrospective studies provided positive evidence for a link between exposure to some cytostatic agents and spontaneous abortion in nurses [26,27], others failed to show an association [28,29]. The first studies were indicative of the potential of cytostatic drugs to induce reproductive effects, but were obtained when handling practices were not properly controlled. A significant association between congenital malformations and exposure to cytostatics has also been suggested [28,30], but no information on safety measures was provided. One recent study failed to find an increase in miscarriages, malformations, low birth weight or preterm birth among nurses handling antineoplastic drugs in a well-protected setting [20]. These results suggest that safety measures can protect health-care workers from the adverse reproductive effects of cytostatics. A significant increase in ectopic pregnancies associated with occupational exposure to these drugs has also been shown [31].

All these results suggest that systemic absorption can occur after handling cytostatic drugs, thus reinforcing the need for careful protection from exposure. In this respect, many recommendations and medical surveillance programs for handling anticancer drugs have been published [16,32–34].

ADVERSE CONSEQUENCES OF EXTRAVASATION

Extravasation of anticancer drugs due to accidental injection or leakage into the extravascular compartment has been reported to occur in 1–6% of treatments in the 1980s [35,36]. A more recent evaluation on more than 3250 treatments documented 24 (less than 1%) cases of extravasation involving vesicant agents only [37].

Local effects ranged from mild erythema (local irritant drug) to severe necrosis at the site of injection (vesicant drug). The lesions may be immediately apparent (pain, erythema, hematoma), but local tissue necrosis usually occurs two weeks (and sometimes more) after extravasation. In the most severe cases, local ulceration or necrosis may be protracted (mainly with anthracyclines) and

Drug	Antidote
Amsacrine	Topical DMSO 50% (v/v) (unproven effect)
Bisantrene	NS
Chlormethine	Sodium thiosulphate 10% (4 ml mixed with 6 ml sterile water)
Dactinomycin	Sodium thiosulphate (as above) (unproven effect)
Daunorubicin, Doxorubicin	Cold compresses, topical DMSO 50% (v/v) and low-dose hydrocortisone
Epirubicin	NS
Mitomycin C	Sodium thiosulphate or topical DMSO 50% (v/v)
Vinca alkaloids	Sodium chloride 0.9%

Table 16.1. *Vesicant agents and proposed antidotes (adapted from Refs. [35,37,39,40])*

debridement followed by plastic surgery is sometimes required to avoid delayed healing. In this respect, critical regions are the dorsum of the hand and antecubital fossa. As the earliest signs heralding extravasation should be recognized, fluorescence microscopy analysis was used as a reliable method for confirmation and delineation of anthracycline extravasation [38].

Cytotoxic drugs most likely to cause severe local necrosis are indicated in Table 16.1. Doxorubicin is the drug most frequently involved in lesions requiring surgical intervention [41]. Paclitaxel was recently included as a possible vesicant inducing moderate soft-tissue injury [42].

Despite the lack of clinical trials, several guidelines have been proposed for the management of drug extravasation. A series of practical steps and putative antidotes to be injected into the extravasation site have been reviewed by Cox et al. [37] and Dorr [35] to limit the extent of tissue damage and to reduce the complications of extravasation. It should be stressed that most antidotes to extravasation which have been proposed, are based on experimental studies or anecdotal case reports and have not been properly evaluated by controlled studies [35].

Non-specific measures should be promptly instituted after immediate cessation of cytotoxic drug infusion. Attempts to aspirate the extravasated drug via the administration catheter may be performed, but this measure is painful and rarely efficient. Other measures are largely empirical and comprise elevation of the limb and bandage to prevent the formation of a hematoma. The application of hot compresses are supposed to be of benefit for extravasation of vinca alkaloids while intermittent ice application is preferred for most other vesicant agents. In most cases, conservative measures in extravasated areas are sufficient to avoid severe tissue necrosis [43].

Other drugs which cause local irritation include aclacinomycin, dacarbazine, etoposide, streptozotocin, teniposide and thiotepa. The status of carmustine, cisplatin, cyclophosphamide, fluorouracil and mitoxantrone remains controver-

sial as extravasation-induced necrosis has been reported as single case reports only [35]. In addition, several drugs, for instance bleomycin, dacarbazine, etoposide, fluorouracil, teniposide, have occasionally caused local phlebitis [35].

POISONINGS WITH ANTICANCER DRUGS

Clinical management

Complex treatment protocols resulting in medication error, inadvertent overdose following miscalculation or mistake in preparation of the drug, and drug interactions [44,45] are the most frequent causes of acute overdose with cytostatic drugs. Intentional overdoses account for a very small number of cases with oral forms. In most cases, symptoms resulting from overdose represent an exacerbation of the pharmacological effects and the predictable toxicities of the offending drug. In addition, several organ toxicities are more drug-specific and may appear as unpredictable reactions.

Beside conservative measures, intensive care and symptomatic treatment, there are no established guidelines on the management of cytostatic overdose. Vomiting can give rise to potentially serious consequences (severe fluid and electrolyte depletion) and requires an aggressive approach to control emesis, especially for drugs with a high emetic potential (see Table 16.2).

Severe	Moderate	Mild
Cisplatin	Cytarabine	Bleomycin
Cyclophosphamide	Hexamethymelamine	Busulfan
Dacarbazine	Procarbazine	Fluorouracil
Dactinomycin	Thiotepa	Hydroxycarbamide
Streptozotocin	Vinblastine	Asparaginase
Chlormethine	Doxorubicin	6-mercaptopurine
Plicamycin	Daunorubicin	Methotrexate
		Mitomycin C
		6-thioguanine
		Vincristine
		Etoposide

Table 16.2. *Emetic potential of antineoplastic drugs (adapted from Ref. [47])*

The management of chemotherapy-induced myelotoxicity [48] is a major step as fatalities after overdoses with such as melphalan, 6-mercaptopurine, methotrexate or vincristine are often related to myelosuppression. The relative degree of myelosuppression induced by several cytostatics is indicated In Table 16.3.

Except for folinic acid rescue in methotrexate overdoses, very few antidotes are available or have been clinically evaluated [49]. Granulocyte-macrophage-

Rare	Mild	Moderate	Severe
Asparaginase	Azathioprine	Fluorouracil	Anthracyclines
Bleomycin	Chlorambucil	Hydroxycarbamide	Busulfan
	Mercaptopurine	Methotrexate	Chlormethine
	Plicamycin	Mitomycin	Cytarabine
	Vincristine	Podophyllotoxins	Dacarbazine
		Procarbazine	Dactinomycin
		Vindesine	Melphalan
			Mithoxantrone
			Nitrosoureas
			Platinum complexes
			Vinblastine

Table 16.3. *Myelotoxicity of antineoplastic drugs (adapted from Ref. [48])*

Possibly effective	Probably ineffective
Carmustine	Anthracyclines (Daunorubicin, Doxorubicin, Epirubicin)
Cyclophosphamide	Cisplatin
Dacarbazine	Cytarabine
Fluorouracil	Dactinomycin
Ifosfamide	Epidophyllotoxins (Etoposide, Teniposide)
Melphalan	Mitoxantrone
Methotrexate	Vinca alkaloids (Vinblastine, Vincristine, Vindesine)
	Mitomycin C

Table 16.4. *Efficacy of hemodialysis on in vivo detoxification of anticancer drugs (adapted from Ref. [53])*

colony-stimulating factor (GM-CSF) has been successfully used in several cases to shorten pancytopenia following cytostatic intoxication [50–52]. *In vitro* dialysability of several cytostatic drugs has been assessed using human plasma [53] and expected *in vivo* detoxification was further proposed, taking into account pharmacokinetic data from the literature (Table 16.4). Cerebrospinal fluid exchange and ventriculolumbar infusion have also been proposed in several cases of intrathecal overdose (cytarabine, methotrexate, vincristine).

Poisonings with antimetabolites

Methotrexate is an antimetabolite structurally related to folic acid which acts as an inhibitor of dihydrofolate reductase. Gastrointestinal absorption is inversely related to the dose, and significantly decreases for doses higher than 20–30 mg/m^2. Bioavailability following intramuscular administration reaches

90%. Approximately 60% of the drug is bound to serum albumin and methotrexate is predominantly eliminated via renal excretion. Several conditions such as previous renal impairment, third vascular space, red blood cell transfusion, hypoalbuminemia and drug interactions especially with NSAIDs, contribute to decreased methotrexate clearance resulting in sustained enhancement of serum methotrexate levels [44,46,54,55].

While conventional doses of up to 50 mg/m^2 are relatively safe, high-dose therapy (>100 mg/m^2) requires folinic acid rescue to prevent multisystemic side effects. Doses of up to 100 mg/m^2 have thus been safely given with folinic acid rescue [56]. However, monitoring serum methotrexate concentrations is highly recommended when doses are above 500 mg/m^2, so that patients with dangerously persistent high concentrations can be rapidly identified.

(1) *Predisposing factors.* More than 50 cases of acute methotrexate intoxication have been reported in the last 20 years. In several cases, overdose occurred using therapeutic doses in the absence of recognized predisposing factors [57,58]. However, most cases have resulted from inadvertent administration of high-dose methotrexate or decreased methotrexate clearance predominantly due to methotrexate-induced acute renal failure. Medication error resulting in unintentional overdose in patients receiving weekly lose-dose therapy is also a possible cause of potential major toxicity [59].

(2) *Clinical symptoms.* Clinical toxicity associated with methotrexate overdose typically includes nausea and vomiting, skin rash with erythrodermia or generalized dermatitis, ulcerations of the gastrointestinal mucosae (polymucositis, ulcerative stomatitis and necroziting enteritis). Protracted but reversible myelosuppression and acute organic renal failure are the major complications. The mechanism of renal injury is not completely understood and may be due to intrarenal precipitation of methotrexate or its metabolite 7-OH methotrexate, or to a direct effect to the glomeruli or the tubuli [58]. Transient hepatic injury and neurological manifestations [55,57] are also observed. Dose-dependent acute hepatitis [60] and interstitial pneumonitis [55] have been seldom reported.

Methotrexate-related fatalities have initially been observed in 6% of patients receiving high-dose methotrexate and were related to myelosuppression leading to sepsis or hemorrhage in 80% of cases, and renal failure in the remaining cases [61]. As stated by Grem et al. [62], the adjustment of dose and the duration of folinic acid rescue has led to a significantly decreased mortality in the range of 1.5 to 2%.

(3) *Management.* The initial management of methotrexate overdose requires intensive supportive care with special monitoring of renal function and urinary pH since excretion of methotrexate by the kidneys is the only effective mechanism to reduce toxicity [62]. Continuous hydration, and urine alkalinization to maintain urinary pH above 7 should be started quickly because methotrexate and its major metabolite are relatively insoluble in the acidic urine. Repetitive oral activated charcoal [63,64] and cholestyramine [65] have also been shown to increase gastrointestinal elimination by interfering with the enterohepatic circulation of methotrexate.

Serum methotrexate concentrations should be measured to manage acute intoxication properly. Different method of assays have been used (see Chapter 2). Results should be interpreted after taking into account the dose administered, the assay method and the time elapsed between methotrexate infusion and serum assay. The severity of methotrexate toxicity is indeed related to the duration of exposure with sustained toxic plasma methotrexate levels above a critical threshold more than to the extent of methotrexate concentration above this level [61,62]. Prolonged exposure ($<0.1\times10^{-6}$ M) during several days can induce methotrexate toxicity. Although this has been debated in several reports, the maximum tolerated serum levels following high-dose methotrexate range from 5×10^{-6} M at 24 hours to 0.5×10^{-6} M at 48 hours and 0.05×10^{-6} M at 72 hours [55]. However, survival has been observed with plasma methotrexate levels of 328×10^{-6} M and 574×10^{-6} M for more than 33 hours respectively [55,66]. Most importantly, renal failure and anuria as a complication of methotrexate intoxication increase the likelihood of sustained toxic plasma levels of methotrexate.

Prompt and massive intravenous folinic acid rescue (up to 1000 mg/m^2 every 3 to 6 hours) is adapted to methotrexate serum levels and repeated until they fall below 0.1 or 0.05×10^{-6} M. Symptomatic treatment and high-dose folinic acid are sufficient in most cases to manage methotrexate intoxication successfully. The role of thymidine, an endogenous nucleoside, as a non-competitive rescue agent was recently reviewed and doses of 8 g/m^2/d by continuous infusion were suggested to be efficient [62]. This regimen has been proposed as an adjunct to high-dose folinic acid, but carefully designed studies to determine the contribution of thymidine in methotrexate toxicity when sufficient dose of folinic acid is used are still lacking.

Several extracorporeal methods have been evaluated to remove methotrexate from the plasma. All these procedures have been regularly debated as removal is often limited by the low extraction ratio of methotrexate [67–69]. Furthermore, the slow redistribution of the drug from tissues into the blood frequently led to rebound to pre-dialysis levels after the procedure is completed [57,58,70]. Plasma exchanges [54] or peritoneal dialysis [67,68] have been shown to be ineffective. However, plasma exchange was proposed as a possible treatment for protracted and moderate intoxication [71]. While the efficacy of hemodialysis has been debated [68], some positive results were obtained [72]. A transient reduction only in plasma methotrexate concentration has been reported after charcoal hemoperfusion [70], but others have described prompt recovery and rapid reduction of serum methotrexate levels [66]. Repetitive charcoal hemoperfusion associated with hemodialysis have also been claimed to be a method of choice in the initial treatment of methotrexate intoxication [57,73,74]. According to several authors, this method should probably be restricted to massive overdoses with high serum methotrexate concentrations, in patients presenting with life-threatening acute renal failure and/or anuria, or after failure of conventional treatment [58,62]. Again, a recent report showed that no significant lowering of methotrexate serum levels and no detectable

concentrations in the dialysate could be obtained after hemodialysis and charcoal perfusion following severe overdose [52].

Although unbound methotrexate is increased by aspirin, clinical results do not support the assumption that aspirin may improve methotrexate removal as intracellular intake of methotrexate is enhanced [71]. More recently, continuous infusion of GM-CSF was successfully used to control life-threatening pancytopenia following severe methotrexate overdose [52]. However, the fact that recovery of white blood cell count was only observed after methotrexate serum levels declined to subtoxic values further emphasized the need to focus primarily on methotrexate elimination.

(4) *Overdose after intrathecal administration* (see Table 16.5). Reports of methotrexate overdose following intrathecal administration have been consistently described in children and represented a unique medical emergency [75–82]. Overdose ranged from 50 to 650 mg (i.e. 4 to 54 times the intended dose) and usually resulted from errors during preparation of the injected solution. While overdoses of intrathecal methotrexate less than 120 mg without significant toxic effects or sequelae have sometimes been reported [75,76, 78,79], fatal acute neurotoxicity with injury to both gray and white matters was observed in the absence of vigorous treatment or in case of delayed treatment [77]. Severe neurotoxicity with coma can also reverse without sequelae [80,81].

Symptoms occur after a short delay and include headache, agitation, meningismus, signs of raised intracranial pressure. Biology of the CSF is consistent with an acute chemical arachnoiditis. Seizures [80,82], or immediate and subsequently fatal necrotizing leuko-encephalopathy after a single 650 mg overdose of methotrexate have also been reported [77]. Finally, instillation of methotrexate via a misplaced intraventricular catheter has resulted in focal encephalopathy, the symptoms of which resolved after shunt removal and systemic corticosteroid administration [83].

Large-dose intravenous folinate administration used to prevent systemic methotrexate toxicity and alkaline diuresis are again the main therapeutic measures. CSF drainage and repetitive exchange of lumbar CSF as soon as possible after the overdose have been suggested as an optimal and safe procedure [75,84]. This treatment is recommended for doses over 7 times the intended dose and should be performed very rapidly because the drug remains in the spinal axis for a short period of time only. Indeed, fatal neurotoxicity was observed despite removal of 80% of methotrexate after a CSF exchange performed within 45 minutes of a 650-mg overdose [77]. Based on a modified single compartment model, Addiego et al. [75] estimated the percentage of methotrexate that can be removed from the CSF as a function of the removed fluid volume and the time elapsed after injection. According to these authors, the drainage of 30 ml CSF within the first 15 min after the overdose is likely to remove more than 90% of injected methotrexate, but recovery will fall to less than 20% of the dose if drainage is performed two hours after injection. However, multiple CSF exchange has been successfully used 3 and 5 hours after a 10-fold intrathecal overdose in two patients aged 4 and 11 years

Age (yr)	Dose (mg)	CSF removal	Delay to CSF removal	Ventriculo lumbar perfusion	Neuro-toxicity	Steroids	Ref.
12	50	yes	60 min	no	mild *	yes	75
4	50	yes	45 min	no	none	yes	75
4	52	yes	10 h	no	none	no	79
2	85	no		no	mild *	yes	76
4	100	yes	5 h	no	none	yes	78
11	120	yes	3 h	no	none	no	78
8	120	no		no	severe **	yes	80
9	625	yes	20 min	yes	severe **	no	81
7	650	yes	45 min	no	fatal	no	77

*Both patients presented only with headache; **both patients recovered without sequelae.

Table 16.5. *Intrathecal methotrexate overdose: summary of reports and treatments*

presenting without signs of neurotoxicity [78]. Only 30% of the whole dose of methotrexate was recovered. No neurotoxicity was observed and neurological examination performed during the following months was normal in both patients.

Because CSF exchange alone was expected to be insufficient following methotrexate overdose larger than 100 mg or in patients who develop acute signs of neurotoxicity, neurosurgical intervention with ventriculo-lumbar perfusion has been considered to complete CSF removal after a long period of time following injection [81,84]. Indeed, complete recovery was observed following such a procedure after a 625-mg overdose [81], while fatal necrotizing encephalopathy was observed in another patient receiving only CSF removal after the same overdose [77]. Eighty-six percent of the total dose was removed within one hour after injection in the first case (85 mg of the drug remained in the CSF), and 80% within 45 min in the second case (138 mg of the drug remained in the CSF).

Corticosteroid administration has been used to reduce the inflammatory component of acute arachnoiditis. The benefit of intra CSF folinic acid administration, which has some epileptogenic properties, has been suggested [80,81] but has not been properly evaluated [84]. Experimental studies in rhesus monkeys have also suggested the potential benefit of carboxypeptidase-G_2 (which hydrolyses methotrexate) as a rescue agent in the management of massive intrathecal methotrexate overdose [85].

Purine analogues. Mercaptopurine (6-MP) and azathioprine, which converts into 6-MP in tissues, are purine analogues. Accidental or intentional overdoses with azathioprine or 6-MP have rarely been reported. The accidental ingestion of 7500 mg azathioprine in a renal transplant patient was followed by minor symptoms, i.e. mild gastrointestinal disturbances (nausea, vomiting and diarrhea), transient liver function abnormalities and a transient fall in leucocyte count [86]. No long-term consequences were noted. After ingesting

1500 mg of 6-MP, a 15-year-old girl only presented with dizziness, frontal headache, abdominal pain and increased serum bilirubin levels [87]. Gastric decontamination with ipecac was performed 90 minutes later. Peripheral blood cell concentration of 6-thioinosine monophosphate rose consistently during the next 3 days while 6-MP was not detected in any sample. Physical examination performed 9 months later was normal. Crystalluria and hematuria have also been reported after doses of 6-MP exceeding 750 mg/m^2 and were expected to be the result of direct renal damage by urine crystals secondary to excessive urinary amounts of unmetabolized 6-MP (88). Fluid loading and alkalinization might thus be discussed in such cases.

These reports suggest that no treatment other than gastric decontamination is required following acute 6-MP or azathioprine overdose. However, a fatal outcome has been associated following chronic overdose in a female patient with hyperthyroidism who was given 600 mg/d 6-MP instead of propylthiouracil during 2 weeks [89]. The patient was admitted for multiple cardiac arrests and presented with hepatic failure and anemia. Seizures further developed and she died on day 3. Autopsy findings revealed bone marrow aplasia and toxic hepatitis. The drug was identified in all tissues using gas chromatography, with the highest concentration found in the blood (110 mg/l).

Pyrimidine analogues

(1) *5-fluorouracil.* No reports of fluorouracil (5FU) overdose have so far been published. Common adverse reactions (i.e. myelosuppression, diarrhea, mucositis) are partly dose-related and are expected in overdoses. Cardiac toxicity (mostly angina pectoris and sudden death) is now a well recognized severe effect of 5FU with an incidence of 7 to 10% during high-dose 5FU therapy [90]. Careful observation of patients receiving inadvertently large doses of 5FU is therefore recommended. Dihydropyrimidine dehydrogenase activity deficiency apparently increases the risk for severe 5FU toxicity [91].

(2) *Cytarabine (cytosine-arabinoside).* Myelotoxicity and severe, sometimes irreversible, cerebellar and cerebral toxicity are common and dose-limiting adverse effects following high-dose cytarabine, i.e total doses higher than 36 g/m^2 [92,93]. Furthermore, cytarabine metabolites play a role in the occurrence of CNS toxicity thereby prolonging neurological dysfunction. Thus, severe and delayed neurological side effects following inadvertent cytarabine overdose may be expected to occur.

Interestingly, an accidental intrathecal overdose of 200 mg cytarabine to a 4-year-old boy treated for acute lymphoblastic leukemia with CNS relapse resulted only in dilated pupils during the first hour [94]. Recovery of 27% of the total dose was possible after CSF exchange with isotonic saline started 1 hour later (50 ml exchanged over 50 minutes). Unsteady gait and mild intention tremor were noted one month later, but long-term neurological follow-up could not be obtained. This report suggested that CSF exchange, if decided upon, should be started as soon as possible after overdose.

Poisonings with alkylating agents

Chlorambucil is an aromatic nitrogen mustard mainly used in the treatment of chronic lymphocytic leukemia. Accidental ingestion or overdosing ranging from 1.5 to 6.8 mg/kg have been repeatedly reported in young children [95-99]. Vomiting and central nervous system toxicity (i.e. lethargy, ataxia and hyperactivity, myoclonic jerks or generalized tonic-clonic seizures with coma in one case) were each noted in the first 3 hours. Neurological signs disappeared during the next 48 hours. Electroencephalogram (EEG) showed paroxysmal discharges reproducing the pattern of petit mal epilepsy and EEG findings persisted several days beyond clinical seizure activity [96]. Moderate and delayed bone-marrow depression was also observed and uneventful hematologic recovery was obtained 3 to 7 weeks later in all cases. These pediatric cases suggested that the immature brain is seemingly at greater risk for developing seizures. Standard gastric decontamination should be performed very shortly after ingestion because the drug is readily absorbed by the gastrointestinal tract.

Further reports in adults confirmed that early generalized seizures are a common feature of chlorambucil overdoses and are not exclusively found in children [100]. Reversible acute renal failure without myoglobinuria was also noted. Finally, no complications other than mild bone-marrow depression were described in another case following the inadvertent ingestion of 280 mg over 5 days [101]. Follow-up examination showed no clinical sequelae in all reports.

Chlormethine. The mutagenicity and venous toxicity of chlormethine, the first nitrogen mustard derivative, has limited its use in Hodgkin's disease. In accordance with its high hematologic toxicity, profound bone marrow depression was recorded after the accidental ingestion of a ten-fold chlormethine dose (58 mg), blood cell count reaching a minimum between day 9 and 12 [102]. Interestingly, severe delayed neurotoxicity with mental confusion, ataxia, amnesia, headache and bladder incontinence developed 5 months later in this patient. Computerized cranial scannography showed hydrocephalus and prompt recovery was observed after surgical shunt into the peritoneal cavity. Intravenous administration of sodium thiosulfate (500 mg/kg) over a long period has been proposed as a protection from chlormethine toxicity [49].

Cyclophosphamide. No report of cyclophosphamide overdose has so far been published. High-dose cyclophosphamide is associated with hemorrhagic cystitis due to the effect of acrolein and the 4-hydroxy metabolites on the bladder epithelium. Early and repeated administration of MESNA reduces the incidence of cyclophosphamide bladder toxicity without affecting its therapeutic activity or systemic toxicity [49]. Phenobarbital and cimetidine, which interact with cyclophosphamide biotransformation, should be withheld after cyclophosphamide overdose [49].

Ifosfamide. Acute encephalopathy is a dose-dependent side effect of ifosfamide administration and was indeed observed after a 25-mg ifosfamide overdose [103]. Interestingly, reversal or prevention of ifosfamide encephalopathy

was observed in two subsequent patients following oral or intravenous methylene blue [103].

Melphalan. High doses of melphalan (100–180 mg/m^2), either alone or in conjunction with bone marrow transplantation (up to 260 mg/m^2), have been associated with bone marrow toxicity within 3 weeks. Experimental studies have suggested that high concentrations of leucine and glutamine may improve melphalan toxicity while arginine and lysine have the opposite effect (reviewed in [49]. The clinical course of a 6-month-old boy who mistakenly received 254 mg/m^2 was marked by pancytopenia, diarrhoea and moderate oral ulceration [104]. Recovery was observed within 1.5 months following continuous hyperalimentation. Unfortunately, no details on the contents in amino acids were given. After the inadvertent continuation of oral melphalan 20 mg/d during 3 weeks (i.e. total dose of 200 mg/m^2 instead of 20 mg daily for 4 days), a patient presented with marked alopecia and severe pancytopenia. Interestingly, blood cell counts returned to normal within only 15 days [105]. Another chronic melphalan overdose (total of 775 mg on 21 days) was marked by severe diarrhea and myelosuppression with prompt recovery over 2 weeks [106].

Cardiac arrhythmia was recently involved in a patient who died 6 days after receiving a single 290 mg/m^2 intravenous melphalan injection [51]. Inadequate ADH secretion and electrolyte abnormalities were the suspected reasons for this early death. Autopsy evidenced bone marrow aplasia and myocardial necrosis Finally, an irreversible acute renal failure occurring 1 day after a 240-mg/m^2 melphalan injection has been reported [107].

Busulfan. High doses of busulfan (4 mg/kg for 4 days) used as preparative regimen for bone marrow transplantation have been associated with generalized seizures in 5 to 10% of patients [108–110]. An additive toxic effect of previous intrathecal methotrexate was also suggested [110]. Prophylactic anticonvulsant therapy initiated several days before high-dose busulfan is therefore recommended but does not always prevent the occurrence of seizures [109]. Other expected toxicities following high-dose busulfan involve the gastrointestinal tract (nausea, vomiting, mucositis, diarrhea), the skin (hyperpigmentation) and the liver (increased serum transaminases). GM-CSF administration has resulted in transiently increased granulocytes in a case of busulfan overdose [50]. Unfortunately, this effect was not sustained after GM-CSF withdrawal.

Nitrosoureas. Dose-related hematologic toxicity is the main limiting factor and the expected toxicity after overdoses of carmustine (BCNU) and lomustine (CCNU).

Isolated cases of reversible bone marrow depression after CCNU overdose have indeed been reported and highlight the finding that massive overdose with CCNU is not necessarily lethal and is reversed by supportive treatment. Following the inadvertent ingestion of 1120 mg over 1 week (instead of 160 mg every 6–8 weeks), a patient presented with minimal nausea only [111]. Severe bone marrow aplasia occurred 2 weeks after the last dose and full recovery was observed after 3 more weeks. This delayed and severe bone-marrow toxicity was further documented in another patient who ingested 600 mg CCNU over

15 days [112]. Again, the patient was asymptomatic during this period and progressively developed pancytopenia over the next 3 weeks. Bone marrow examination was normal 1 month later and in several examinations performed up to 4 years after the overdosage. This report also provides evidence that cells producing colony-stimulating activity are fairly resistant to high-dose CCNU. Enhanced myelosuppressive effects of carmustine have been suggested in cimetidine-treated patients, so that cimetidine should probably be avoided following carmustine overdose [113].

Poisonings with vinca alkaloids

Vincristine. The neural tissue is particularly susceptible to the effects of vincristine, a microtubular poison which is bound primarily to tubulin. Following intravenous infusion, the drug rapidly binds to plasma proteins and tissue elements where concentrations are much higher than that in the serum.

(1) *Intravenous overdose.* A large body of experience has now been accumulated for adults or children following acute intravenous vincristine overdose [114–124] or subacute exposure over consecutive days [125]. All these reports have highlighted the serious toxicity of massive overdose. Vincristine overdose ranged from 0.12 mg/kg to 0.60 mg/kg. A characteristic clinical syndrome developed within 2 days. The earliest and most consistent findings are nausea, vomiting and decrease or loss in deep tendon reflexes. Paresthesias, muscular weakness and generalized pain developed within the first week. This dose-related peripheral neuropathy slowly resolved over 1 to 2 months, but minimal sequelae have sometimes been noted [115,118,120,122]. Signs of central nervous system toxicity (mental confusion, amnesia) with slowed electroencephalogram were usually noted, and disappeared over several weeks. However, Casteels-Van Daele et al. [116] reported persistent brain damage up to 2 years after overdose. Generalized seizures are consistently observed and may occur up to 10 days after acute overdose [118,124]. The autonomic nervous system is also affected with symptoms of paralytic ileus or bladder atony. Hyponatremia related to an inappropriate antidiuretic hormone secretion frequently developed within the first week and probably resulted from the direct stimulation of hypothalamic nuclei. This may also explain the occurrence of fever and seizures [118,123]. Moderate or life-threatening bone marrow aplasia is consistently observed after 4 to 7 days and reverses within 3 weeks.

Other symptoms include diarrhea with severe fluid loss, alopecia, and orthostatic hypotension, but mild hypertension is also sometimes observed [119]. Increase in hepatic transaminases has been noted in several cases [120] and were assumed to represent a possible indicator of severe outcome after vincristine overdose [119]. Finally, myocardial toxicity has been suggested in an isolated case with increase in MB-CPK, sinus tachycardia and premature ventricular contraction [120].

Although symptoms of vincristine overdose are close to the well-known reported chronic toxicity, symptoms are much more severe. Fatalities directly

related to vincristine toxicity have been reported in 4 of 18 cases and resulted from complications of myelosuppression and cardiac arrest [118,119]. Since deaths have mostly been related to bone marrow depression, recovery can reasonably be expected in patients surviving the critical phase (Table 16.6). Indeed, except for isolated cases of persistent minimal neuropathy [115,118, 120,122] or brain damage [116], no permanent sequelae have been attributed to vincristine overdose in the remaining cases.

No specific antidote has so far been evidenced. Although folinic acid rescue (120 to 144 mg/d for 2 or 3 days) was argued to reduce acute vincristine toxicity and shorten the duration of symptoms [117,119], experimental or clinical evidence that folinic acid is an effective treatment remains poor and controversial [114,122,123]. In two patients who received a similar dose of vincristine (6 mg/m^2) and who were observed under similar conditions, the clinical outcome was seemingly not different in the only patient who received folinic acid [114]. The administration of oral glutamic acid 1500 mg daily together with vincristine treatment has also been shown to significantly decrease vincristine-associated neurotoxicity in a therapeutic trial [126]. Although the mechanism of this preventing effect is unknown and requires further investigation,this treatment can be considered in acute overdose.

Although the beneficial effects of folinic acid remain to be established, conventional treatment following vincristine overdose routinely include intravenous folinic acid rescue, as in methotrexate overdose, prophylactic antiepileptics, close medical monitoring with surveillance for infection and supportive treatment [119]. Hyponatremia usually resolved after fluid restriction as required. Since vincristine cannot be dialysed and because of elevated vincristine protein binding, plasmapheresis or exchange transfusion were performed 6 hours after overdose to increase vincristine clearance [119,121]. Early results suggested this procedure may contribute to a favourable outcome in 3 out of 4 patients, with more than a 50% decrease of pre exchange levels. In the last case, the amount of vincristine removed was 7.6% only, and the patient died on day 9 [119].

(2) *Intrathecal overdose.* Because of its high neurotoxic potential, vincristine should be strictly administered via the intravenous route. Several reports have indeed stressed the extremely high severity of inadvertent intrathecal administration, with a fatal outcome in most cases [127–134]. Clinically, patients presented with signs of myeloencephalopathy within 1 or 2 days. The course was later roughly similar in all patients, with severe headache, ascending motor paralysis, bladder paresis, respiratory paralysis, sensory loss, seizures and coma with slowed EEG. Among the eight reported cases, fatal outcome due to progressive damage to the nervous system occurred between day 3 and day 36 in 6 patients who inadvertently received 0.68 to 3 mg intrathecal vincristine. Post-mortem examination showed swollen neurons with aggregates of neurofilaments or acidophilic cytoplasmic crystals in the motor neurons of the spinal cord and brain stem, very similar to the pathologic findings in experimental models of vincristine neurotoxicity [131,133]. Others have found total neuronal loss with tissue necrosis in brain regions directly in contact with CSF [134].

Age	Dose in mg (mg/kg)	Outcome	Treatment (other than supportive)	Ref.
7	? (0.12)	Persistent paresthesias and abdominal cramping		118
5	3.5 (0.20)	Recovery		118
2	4 (0.25)	Recovery		124
3	5 (0.26)	Recovery	Exchange transfusion + folinic acid	119
8	6.5 (0.25)	Death on day 24 (*Candida* infection)		118
5	7.5 (0.2)	Death on day 9 (cardiac arrest)	Exchange transfusion + folinic acid	119
9	8.5 (0.18)	Recovery	Exchange transfusion + folinic acid	119
4.5	8.75 (0.43)	Permanent neurologic sequelae		116
28	9	Recovery		114
42	10	Recovery	Folinic acid	114
55	10	Persistent mild neuropathy (unexplained death on day 116)		115
14	10	Recovery	Folinic acid	117
7	13.5 (0.6)	Death 68 hours after (hemorragic complications)		118
14	15	Recovery (neuropathy lasting 5 months)	Folinic acid	123
18	16	Recovery	Plasmapheresis	121
44	24 (0.4)	Persistent peripheral paresthesias		120
24	25 (0.39)	Persistent mild neuropathy	Folinic acid	122
13	32 (0.6)	Death 33 hours after (hemorragic complications)		118

Table 16.6. *Summary of outcome and treatment of vincristine overdose*

Prolonged survival with permanent coma over 11 months was observed in one case after initial CSF drainage and aggressive supportive care [127]. Serial electrophysiologic studies showed persistent EEG activity in the alpha range with progressive decrease in amplitude during the following 10 months.

Repeated CSF drainage and parenteral folinic acid have never proved to significantly alter the outcome after intrathecal vincristine [127,129,131,132]. Successful management was obtained in an adult patient who received 2 mg intrathecal vincristine [128]. Immediate CSF exchange associated with continuous CSF removal using subarachnoid space washout allowed a 95% recovery of injected vincristine. Later on, 10 g over 1 day intravenous glutamic acid were administered followed by an oral dose of 1.5 g daily. The patient presented with residual lower-extremity neuropathy but long-term evaluation was not

possible as the patient died three months later from his primary disease and the respective role of CSF drainage and glutamic acid could not be assessed. Because vincristine is rapidly and extensively bound to brain tissue after inadvertent intrathecal administration, CNS drainage or CNS washout should be performed within minutes. As a matter of fact, vincristine levels in the lumbar subarachnoid space were 14,000 ng/ml 30 minutes after 1.2 mg intrathecal vincristine [132], and 830 ng/ml 4.5 hours after 0.68 mg [129] However, a rebound in vincristine CSF concentrations, due to reversible binding to the brain tissue, can be observed after the washout is stopped [129].

Other vinca alkaloids. The acute toxicity of other vinca alkaloids has been described only as single case reports with toxic effects very similar to those observed following vincristine overdose [135,136].

Unexpected symptoms associated with a ten-fold overdose of vindesine consisted successively of tinnitus, impaired swallowing, sphincteric incontinence, hiccups, peripheral neuromyopathy, fever, and anuria [135]. Hematotoxicity was observed on day 3 and reversed 10 days later. Vinblastine overdose was associated with the clinical picture including gastrointestinal disturbances, hematologic toxicity, adynamic ileus, areflexia, seizures and coma [136].

In both cases, supportive treatment, parenteral nutrition and folinic acid administration resulted in complete recovery within 3 months. Again, folinic acid and corticosteroid use remain controversial. Experimental data have suggested that aminoacids infusion including glutamic acid, aspartic acid, ornithine, citrulline and arginine reverse the cytotoxicity effect of vinblastine [49]. The last three aminoacids have been used by Fiorentino et al. [135] but their efficacy cannot be fully evaluated.

Antitumour antibiotics

Dactinomycin. A single case of accidental overdose has been reported in a 17-year-old patient [137]. Two days after the inadvertent repeated administration of dactinomycin (total dose of 3.3 mg/m^2), he had a generalised convulsion associated with hyponatremia, hypokalemia, hypocalcemia and hypomagnesemia. Later on, the patient developed bone-marrow suppression, profuse diarrhoea, severe oral mucositis, generalised oedema together with severe erythema (radiation recall) and hepatic dysfunction. Treatment was supportive and full recovery was observed after 3 weeks.

Anthracyclines (doxorubicin). The most significant toxicity associated with conventional anthracyclines doses is delayed cardiotoxicity. However, acute symptoms including arrhythmias, heart block, benign pericardial reactions, change in blood pressure and decrease in ejection fraction may occur within 24 hours after high doses, while chronic anthracycline cardiotoxicity with congestive heart failure is related to a cumulative dose of 550 mg/m^2.

Twelve acute accidental doxorubicin overdoses over a 14-year period have been reported by Curran [138]. Intravenous doxorubicin doses ranged from 3 to 10 times the intended dose. Leucopenia and pancytopenia were noted in all

patients. Mucositis developed in 7 patients and lasted 2 to 6 weeks. Isolated seizure occurred once. Rash, cracked nails, increased serum creatinine levels and transient peripheral numbness were also reported. Seven patients survived and death occurred in the other 5 patients from within less than 24 hours to 16 days after the overdose, for doses ranging from 150 to 333 mg/m^2. Two patients developed heart failure before death. Autopsy findings included lung edema and a dilated left ventricle in one case. Complete recovery was observed following a 10-fold overdose (230 mg/m^2) in a patient treated with hemoperfusions. Such a procedure is thus expected to reduce doxorubicin serum levels, but should be performed within minutes after overdose as doxorubicin is highly bound to proteins.

As doxorubicin is extremely irritating to tissues, it is mainly used intravenously. Indeed, after erroneously receiving an intrathecal dose of doxorubicin, a 12-year-old female patient complained of rapidly reversible fever, headache and vomiting [139]. No measures were taken to remove the drug. Two weeks later she presented with acute and severe encephalopathy. Further investigations noted a damage to the blood-brain barrier, high-pressure tetraventricular hydrocephalus and mild diffused periventricular leucoencephalopathy. Complete reversal was obtained after ventriculo-peritoneal shunting. A nine-month follow-up showed no neurological abnormalities.

Bleomycin. No acute intoxication has been reported. As the drug is mainly eliminated via the kidney and its toxicity is enhanced by renal dysfunction, concurrent administration of nephrotoxic drugs should be avoided in case of overdose [49].

Miscellaneous agents

Asparaginase. Although reports of asparaginase overdose have not been found in the literature, severe and protracted brain toxicity (i.e. lethargy, somnolence, coma) can be expected [49]. Continuous infusion of asparagine (1–2 mmol/kg/d) has been shown to reverse brain dysfunction.

Cisplatin. Impairment of renal function is a major dose-limiting toxicity of cisplatin doses larger than 100 mg/m^2. Careful parenteral hydratation before, during and after drug administration is crucial to avoid severe renal injury. Doses larger than 180 mg/m^2 have also been associated with disabling neurotoxicity and loss of hearing.

Indeed, acute overdose may result in severe complications, as recently summarized [142]: gastrointestinal toxicity with intractable vomiting, acute renal failure, liver failure, deafness, ocular toxicity, neuritis, myelosuppression and death might be expected. Complete clinical description was provided in one report following the accidental administration of a total dose of 480 mg/m^2 over 4 days [143]. Neurotoxic manifestations with peripheral neuropathy, dysarthria and decreased hearing were noted within the first week. Acute oliguric renal failure was present on day 6 and required hemodialysis for one month. Maximum myelosuppression was recorded during the second week. The

calculated half-life of the platinum elimination phase was 28 days for plasma, and no platinum was detected in the fifth month. Neuropathy, nephrotoxicity and myelosuppression resolved following general supportive measures. However, the patient suffered permanent bilateral deafness with no significant improvement 18 months later. Regressive loss of visual acuity and color perception associated with a persistent negative-type electroretinogram has been well-described after inadvertent cisplatin overdosage [144]. Life-threatening gastrointestinal and myelotoxicity without significant ototoxicity or neurotoxicity have been noted in a six-month-old infant erroneously given 450 mg/m^2 cisplatin [145]. Interestingly, prolonged severe renal tubular acidosis without renal failure developed. This report suggested a wide age-related difference in the toxicity of cisplatin.

Acute respiratory failure with severe hypocapnia and acid base disturbances were also described following an inadvertent cumulative dose of 450 mg in 3 days [146]. This life-threatening hypocapnia required mechanical ventilation for 8 days. Although CNS penetration of the drug is limited, the authors suspected a direct effect on the respiratory centre, leading to hyperventilation.

Massive accidental overdose following the inadvertent administration of cisplatin instead of carboplatin has recently been reported [147]. The patient received cisplatin 280 mg/m^2 without hydratation and experienced severe vomiting from the second day, myelosuppression, irreversible renal failure, progressive hearing loss and optic neuritis. Other unusual symptoms consisted of hallucinations, grand mal seizures and liver toxicity. She recovered but underwent a kidney transplant 6 months later because of renal failure requiring dialysis. Moreover, profound deafness was also still present 25 months later.

No specific management proved to be effective in cisplatin overdose. Prophylactic hemodialysis was shown to be ineffective since the drug is highly and rapidly bound to plasma proteins [148]. However, plasmapheresis was recently suggested to be effective in lowering blood platinum concentrations and improving the clinical status of one patient, providing indirect evidence for a pool of exchangeable cisplatin [147]. Although no antidotes have been established after overdose in humans, experimental studies have shown that the thiol agents N-acetylcysteine, sodium thiosulfate, sodium diethyldithiocarbamate or fosfomycin may limit nephrotoxicity and/or ototoxicity [49,147,149]. Confirmative studies in humans are warranted. Delayed intensive hyperhydratation and repeated administration of sodium thiosulfate, which combines with platinum, was recently claimed to prevent the occurrence of acute renal failure after a 240 mg/m^2 cisplatin overdose [150]. This result is supported by a study showing that concurrent administration of thiosulfate can result in at least a twofold increase in cisplatin therapeutic dose (up to 225 mg/m^2) with substantial kidney protection and without altering the pharmacokinetics of cisplatin [151].

Mitoxantrone. Mitoxantrone is a synthetic anthracendione structurally related to the anthracyclines doxorubicin and daunorubicin, but with lower cardiotoxicity. Accidental overdose (100 to 183 mg/m^2) has been reported in four adult patients [153,154]. All had severe but reversible myelosuppression.

Other adverse effects included early gastrointestinal symptoms (nausea, vomiting, anorexia), chills, lumbar pain, and transient amylasemia in one patient. All four patients fully recovered. No immediate cardiotoxicity was observed, but one patient previously exposed to extensive daunomycin regimen developed congestive heart failure four months after overdose [154] suggesting an additive effect of mitoxantrone to preexisting myocardial damage. Long-term cardiac follow-up was not possible in the other three patients. A further case of mitoxantrone inadvertent bolus injection of 100 mg/m^2 has also been reported in a 9-year-old girl [155]. Nausea and headache were observed a few hours after the overdose and severe myelotoxicity was evident again after one week. Repeated echocardiography showed a progressive but asymptomatic decrease in myocardial contraction at 3 weeks and a complete normalization was spontaneously observed 6 months later.

Treatment of mitoxantrone overdose is only supportive. Although mitoxantrone is rapidly sequestered in tissue compartments, charcoal hemoperfusion was carried out in one case [155]. As expected, no significant effect on drug clearance was observed and total elimination of the drug occurred only after 18 days. Late appearance of cardiovascular abnormalities could not be excluded in view of these cases and prolonged cardiac surveillance should be thus recommended.

Podophyllin. Podophyllum resin is obtained by alcohol extraction from the roots of *podophyllum peltatum* or *emodi*. Podophyllin preparations, initially used as oral cathartics, are now used for the topical treatment of verruca vulgaris and condyloma accuminata. The drug is available as ointment, paint or solution containing up to 20% podophyllum resin (i.e. 5 g podophyllin for a 25-ml solution). Topical application could result in significant absorption especially when applied over a prolonged period on large areas or to altered skin. Podophyllotoxin, a highly soluble beta-D-glucoside, is thought to be the major active ingredient of podophyllin (which contains approximately 20% podophyllotoxin) and is eliminated in the bile with a half-life of 48 hours.

The DL_{50} of podophyllotoxin is 33 mg/kg in mice and 15 mg/kg in rats. In humans, the expected toxic dose is about 300 mg/m^2. Recent experimental data in rats have reproduced various histopathological changes in the neurons, liver, intestine, testis and pancreas of animals receiving podophyllotoxin at doses of 5 to 15 mg/kg, all of which correlate well with the clinical symptoms observed in intoxicated humans [157,158].

Following the first report by Prentiss in 1882 [159], more than 30 cases of systemic podophyllin poisonings have been published [160–178]. About one half resulted from accidental or intentional oral ingestion and the other half from topical application of podophyllin resin, mainly on genital condyloma accuminata. More recently, therapeutic or prophylactic drinking infusions made from the traditional Chinese herbal medicine Bajiaolian (*Dysosma pleianthum*) or Guijiu (*Podophyllum emodi*) have been reported as another cause of podophyllin or podophyllotoxin intoxication [179,180]. Reports mostly involved adult female patients; pediatric cases have been seldom described [161,170].

(1) *Clinical symptoms.* The onset of symptoms was usually rapid after oral ingestion. First clinical manifestations appeared within 2 hours and included gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain) which appeared in 90% of cases. Initial manifestations may be delayed 12–24 hours following cutaneous application [162,171,174]. Later on, autonomic dysfunction (fever, orthostatic hypotension, tachycardia, tachypnea), oliguria and urinary retention developed. Bone marrow suppression with marked thrombocytopenia were sometimes observed during the first week and reversed in 3 weeks [160,162,168,169,175,180]. Bone marrow biopsy showed decreased mature marrow elements with cytoplasmic vacuolation of myeloid precursors and increased numbers of mitotic figures while megakaryoctes were unexpectedly normal [169]. On the other hand, early leucocytosis (above 20,000/mm^3) followed by leucopenia have also been reported [160,162,171,174,180]. Transient renal failure [162,177], abnormal liver function tests or toxic hepatitis [160,168,174,175,180] and increased serum amylase [180] have been described. Intravascular disseminated coagulation is seldom reported [164].

The most striking clinical feature of systemic toxicity is central and peripheric neurotoxicity in more than 70% of patients. Central nervous system involvement ranged from mild confusion or obnubilation to severe coma which developed several hours after intoxication. Hypotonia, visual or auditory hallucinations, delirium and psychosis have also been reported [166,176,180]. This toxic encephalopathy was usually transient and reversed over several days [162,166,171], but prolonged deep coma [164,180] with fatal outcome [162,178] also occurred. Permanent impairment of mental function has been seldom reported. Whereas CT brain scan may be normal in the acute phase of encephalopathy, further development of irreversible cognitive dysfunction with dilated ventricles and diffuse cerebral atrophy on magnetic resonance imaging (MRI) was reported 1 year after an acute oral intoxication [163]. Chapon et al. [164] also reported such MRI findings 2 months after acute intoxication in another patient. Severe neurologic damage involving both the central and peripheral nervous system with developmental delay has been described 2 years after accidental poisoning in a 18-month old male [170].

Progressive sensorimotor peripheral neuropathy and autonomic neuropathy were observed in 70% of all cases. The toxic neuropathy develops following the acute phase or may be delayed. Peripheral neuropathy was sometimes limited to paresthesias or sensory ataxia which peaked on day 5 to 7. The cerebrospinal fluid was usually normal, and elevated proteins has been seldom noted in parallel to the evolution of neuropathy [164,165]. Clinical and electromyographic signs were consistent with axonal sensorimotor and autonomic peripheral neuropathy [160,164,166,172]. In some cases, nerve biopsy evidenced loss of myelinated fibers, axonal degeneration with type E teased fibers, swelling of Schwann and endothelial cells [164,172]. Neurological disturbances improved slowly over several months [160,166,180] but persistent residual peripheral deficit has been noted 16 to 18 months later [165,172]. Clinical improvement was often observed while EEG signs continued to worsen [160]. Autonomic

neuropathy consisting of hyperthermia, sinus tachycardia, orthostatic hypotension, polypnea, urinary retention, acute gastric dilatation or paralytic ileus were also frequently observed [166,173,175].

Fatalities occurred in 4 (13%) cases among 30 reported intoxications and were observed after accidental or intentional oral ingestion in 3 cases [162,178, 181], or after large cutaneous application in one case [177]. Fatal dose ranged from as little as 325 mg [181] to 11 g [178] with death occurring within 31 hours to one week. Survival has also been observed with doses of 2 g up to 6 g [160,165,172,173,180]. However, mild but persistent neuropathy was still present several months later and was the most disturbing sequelae of podophyllin intoxication.

(2) *Management*. Basically, the management of podophyllin intoxication is conservative and no specific antidote has been identified. Gastric decontamination and activated charcoal administration are supposedly efficient when performed rapidly after oral ingestion. Massive and repetitive charcoal administration should be used with caution because of a possible occlusive syndrome requiring surgery [160]. Hemodialysis is not indicated because the drug is lipid soluble [174]. Hemoperfusion has been suggested to improve immediate clinical outcome in several patients [167,171,174], but was unable to prevent death in another patient [162]. Indeed, recovery of podophyllotoxin does not exceed 10% of the expected ingested dose after hemoperfusion [167]. Furthermore, a recent report emphasized the potential risk of life-threatening bleeding during hemoperfusion related to the exacerbation of podophyllin-induced thrombocytopenia [180].

Epidophyllotoxins. Pawlicki et al. [140] suggested that oral etoposide overdose is not associated with life-threatening reactions. The reported patient had inadvertently taken 200 mg etoposide during 25 days (total dose 4900 mg) and presented only with persistent slight myelosuppression and biological signs of immunosuppression (i.e. decreased leucocyte and T lymphocyte counts, and reduced blast transformation) over 57 months. Another report of two patients incriminates high-dose etoposide (total cumulative dose of at least 6800 mg/m^2 over 4 cycles) as a cause of toxic hepatitis [141]. Liver dysfunctions were clinically apparent 3 weeks after the last dose of etoposide and resolved spontaneously over the next 12 weeks.

Procarbazine. Doses higher than 3 mg/kg for 14 days are associated with reversible myelosuppression. One case of persistent thrombocytopenia lasting 40 months was however reported, following inadvertent continuation of procarbazine, 150 mg daily for 25 days (152).

Taxol. Taxol, an alkaloid extracted from the bark of *Taxus brevifolia* or other Taxus (yew) species is now available as an antineoplastic drug. The extreme severity of Taxus poisoning has been recently emphasized in the report of five sudden unexpected deaths following suicidal Taxus ingestion [156]. Indeed, yew extracts are extremely cardiotoxic (see Chapter 31).

ACUTE POISONINGS WITH IMMUNOMODULATING AGENTS

Cyclosporin

Cyclosporin is an immunosuppressant agent, widely used in organ transplantation, and recently approved in rheumatoid arthritis and psoriasis. The manufacturer has recently reviewed the current experience on cyclosporin overdoses, based on previous published data or spontaneous reports received by Sandoz Drug Monitoring Centre up to April 1991 [182]. Altogether, 29 episodes of acute overdose in 27 patients were described, and included 20 oral and 7 parenteral overdoses. All but one parenteral overdose was recorded in premature neonates following intramuscular (5 cases) or intravenous (1 case) administration. Accidental overdose was the major cause of intoxication, accounting for 23 cases, whereas intentional overdoses accounted for 4 episodes only. Overall, doses ranged from 20 to 400 mg/kg, with a maximum of 10 g as a single dose. Clinical data was available for 24 patients.

Interestingly, no consequences were observed following ingestion of doses ranging from 20 mg/kg to 104 mg/kg in 7 patients. Minor clinical or biological manifestations were recorded in 12 patients and consisted of transient hypertension, tachycardia, severe headaches, drunken feeling, and gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea). Renal function remained unchanged in 11 patients, and 3 others, with previously impaired renal function, presented with slightly increased serum creatinine levels. The remaining 7 patients were neonates. Hyponatremia and/or transient oliguria without change in renal function were observed after intramuscular injection in 4 neonates less than 44 days old. Life-threatening reactions were noted in only 3 pediatric patients. A 2-month-old patient presented with hypotension, wheezing, palor and tachycardia following 240 mg cyclosporin orally, and a neonate developed cyanosis, metabolic acidosis, respiratory depression and oliguric renal failure after infusion of 400 mg/kg cyclosporin. A fatal outcome was noted in a severe premature neonate who exhibited metabolic acidosis and worsened renal function after a 179 mg/kg intramuscular injection. Post mortem concentrations of cyclosporin showed very large amounts of the drug in the liver and kidney.

These data suggest a low acute toxicity of cyclosporin in humans, with complete recovery in most if not all cases. Favourable outcome was also reported after long-term overdose (550 to 3,200 mg/day over 8 days) in two patients who only presented with gastrointestinal disturbances, elevated serum creatinine level and/or urinary retention [183,184]. The calculated cyclosporin half-life was 91 hours. However, it should be stressed that more severe intoxication has been recorded in premature neonates and/or after parenteral overdose. The highest blood cyclosporin concentration recorded was 13,050 mg/l after a 400 mg/kg intravenous injection, and the approximate calculated half-life after acute overdose ranged from 2.5 to 23.5 hours in adults, and up to 58 hours in neonates.

Basically, the proposed management of cyclosporin overdose included cyclosporin discontinuation, monitoring of clinical status and renal function, and symptomatic measures as required. The absence of a clear relationship between cyclosporin blood concentrations and clinical symptoms does not support the benefit of blood level determination in the management of poisoning. Gastric decontamination using emesis-inducing medication was proposed as the first-line therapy after oral overdose [182]. Activated charcoal plus sorbitol administration was suggested to be effective up to 6 hours after oral overdose [185]. However, activated charcoal has no proven efficacy in cyclosporine overdose and its use has been challenged by others until reports of further experience are available [182]. Furthermore, based on pharmacokinetic considerations and limited experience, plasmapheresis appears to be of limited value and cannot be recommended. Similarly, total blood exchange, performed in 2 neonates has no proven effectiveness.

FK 506 (tacrolimus)

Although tacrolimus is not chemically related to cyclosporin and clinical experience is still limited, current data do not suggest a different profile of toxicity [186]. Therefore, acute overdosage is expected to be similar to that of cyclosporin.

Interferons

Several acute adverse effects following interferon treatment are clearly related to the dose and are significantly increased with doses over 18 MU/day. Most important are gastrointestinal disturbances, cardiovascular symptoms (i.e. hyper- or hypotension and tachycardia), fatigue and central nervous system toxicity [187]. In the most severe cases, patients are frankly encephalopathic, and lethargy or (very rarely) coma has been described with dosage higher than 50 MU/day. Laboratory abnormalities after high doses included mild hepatotoxicity, leucopenia and thrombocytopenia.

Interleukin-2

Interleukin-2 (IL-2), a lymphokine produced by all phenotypes of T lymphocytes, is increasingly used to treat patients with cancer refractory to conventional treatment. Differences in toxic effects seemed to be related to IL-2 dose and/or the schedule of administration [188]. The most common dose-related adverse effect reported in patients receiving IL-2 is the flu-like syndrome with generalised malaise, fever and chills, which is usually observed few hours after administration. Other dose-related events are neuropsychiatric complications with moderate or severe behavioural changes, cardiovascular complications with hypotension and cardiac arrhythmias responding to conventional treatment, weight gain above 10%, acute renal failure, anemia and thrombocytopenia.

Furthermore, the incidence of IL-2-associated hypothyroidism has been noted to be higher following a multiple course of therapy. The most serious adverse effect is the vascular leak syndrome with extravasation of plasma proteins and fluid from capillaries into the extravascular space. Clinically, it is marked by generalised oedema, weight gain, cardiopulmonary complications and renal failure. Management of IL-2-induced toxicities is mainly conservative and most complications are reversible with symptomatic treatment. Patients with hypotension may be treated with foot elevation and prudent fluid replacement with crystalloid or colloid solutions, or low dose dopamine. Arrhythmogenic vasopressors should be avoided and phenylephrine is preferred if the patient remains hypotensive or develops tachycardia.

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Human Toxicology, J. Descotes (Ed.)

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17. Selected over-the-counter drugs

In the United States over-the-counter (OTC) drugs comprise a 12-billion dollar industry made up of hundreds of thousands of products. Besides causing a significant number of acute and chronic poisonings each year, OTCs are linked to drug and micronutrient interactions, excipient-related reactions and drug abuse [1–6].The size and complexity of possible adverse reactions associated with OTCs makes reviewing them in a comprehensive manner beyond the scope of a single chapter.

We have chosen to focus on three OTCs that we believe are particularly hazardous when accidentally ingested by children. We have selected prenatal strength iron, loperamide, and imidazoline derivatives because there is a high incidence of accidental poisoning associated with each of these medications, as well as a high potential for life-threatening events to occur as a result of the exposure. In our opinion these medications are more dangerous than OTCs that are ingested more frequently but rarely cause serious toxicity (i.e. cough and cold preparations). They are also more dangerous than OTC products that contain potent poisons rarely encountered by children because of lack of availability, product formulation, or product packaging (e.g. camphor-containing liniments).

IRON

Iron is the most frequent cause of medication-related fatalities in the pediatric population in the United States. In 1991, 25% of pediatric fatalities reported to the American Association of Poison Control Centers National Data Collection System were due to prenatal strength iron [7]. This experience has been shared by other countries such as Australia and South Africa, and will continue as iron supplementation increases in developing countries [8,9]. Other factors which fuel pediatric iron poisoning are the bright color and sweet taste of these preparations, public and professional ignorance of their toxicity, widespread over-the-counter availability, and bulk packaging in large quantities.

Iron is available as tablets and capsules (both normal and extended release), solutions and suspensions. The elemental iron content of the preparation

Iron salt	Elemental iron (%)	Common preparation strength (mg)	Elemental iron per tablet (mg)
Ferrous sulfate	20	325	60
Ferrous Gluconate	12	325	39
Ferrous Fumarate	33	320	105

Table 17.1. *Percentages of elemental iron contained in common iron preparations*

varies according to the salt form used (Table 17.1). It is important to know which salt form is involved in a suspected poisoning since dose–response relationships are based on elemental iron.

Toxicity

Estimates of the lethal dose of elemental iron range from 180–300 mg/kg [10]. The smallest fatal dose in an adult was 2 g of elemental iron (50 tablets of 200 mg ferrous sulfate) in a 20-year-old female. This patient presented 24 hours after ingesting the iron as a suicide attempt. She was treated with fluid replacement, sodium bicarbonate, intravenous and intraperitoneal deferoxamine, and peritoneal dialysis, but succumbed 48 hours after the exposure [11]. The smallest lethal dose in a child was 600 mg. This 19-month-old female patient ingested 15–16 200-mg ferrous sulfate tablets and was treated with salt water as an emetic in a local hospital. She was sent to another hospital for admission but ended up being sent home. The child died four hours after the ingestion [12]. At the 50th percentile for weight, the child ingested 54.5 mg/kg.

Mild toxicity, characterized by nausea, vomiting, diarrhea, headaches, and lightheadedness, develops at doses as low as 10–20 mg/kg [13,14]. There is a progression from gastrointestinal complaints to systemic toxicity in the range of 40–60 mg/kg [15].

Pathophysiology

Iron is essential for production of heme and key enzyme systems, yet it is an extremely toxic cellular poison, acting as a co-factor for generation of free radicals. Thus, iron's presence in the body is tightly controlled. At any given time there is only 1–2 mg of iron mobilized from stored iron. Stored iron is sequestered into the center of large spherical proteins called ferritin, thereby preventing reactions with cellular constituents. Normally, 80% of the body's burden of iron is present as hemoglobin, 25% as stored forms of iron (50% ferritin, 50% hemosiderin), 5% as myoglobin, and less than 5% as enzymes and transferrin.

There are no mechanisms for controlling body excretion of iron so hemostasis is maintained strictly by controlling absorption of iron. Typically, 0.6 mg per

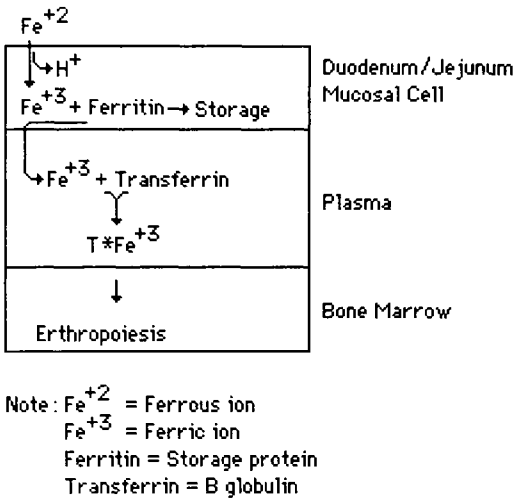

Fig. 17.1. A simplified schematic of iron absorption from the intestinal lumen to systemic circulation.

day are lost by males and 1.2 mg per day by females. Absorption of inorganic iron occurs in the duodenum and proximal jejunum via an active transport mechanism. Ferrous iron($^{+2}$) is taken up by the absorptive cell, oxidized to ferric iron ($^{+3}$) and sequestered as ferritin for storage if not immediately needed. Iron may be released from ferritin in the absorptive cell and may be passed on to transferrin in the intestinal circulation when needed. Transferrin takes the iron either to erythroid precursors in bone marrow or to the hepatocyte for storage (Fig. 17.1) [16].

During an overdose, the active transport system becomes saturated and there may be significant influx of iron into systemic circulation via first-order passive absorption [17]. Transferrin binding sites become saturated and the 'free' iron is taken up by the liver, heart, and kidney. In these target organs, iron probably forms free radicals through the reaction [18]:

$$Fe^{+2} + H_2O_2 \rightarrow Fe^{+3} + {}^{\bullet}OH + {}^{-}OH$$

Highly reactive hydroxyl free radicals react with unsaturated lipids in the mitochondria to eventually cause cell death.

Clinical course

The clinical course of iron poisoning has five phases:

– **During the first phase** (0–6 hours post ingestion), gastrointestinal symptoms predominate. Most patients develop nausea, vomiting, abdominal cramping and diarrhea. Vomitus may be blood-tinged and stools may have a black tarry appearance. Polymorphonuclear leucocytosis (WBC > 15 000 mm^3)

and hyperglycemia (>150 mg/dl) often occur, presumably as an inflammatory response to gastrointestinal injury. In high concentrations, iron acts as a corrosive, so gastrointestinal perforation with subsequent exsanguination can occur [19,20].

Another direct effect of iron that may occur during this phase is reversible coagulopathy. Tenenbein and Israels [21] described two patients with severe iron poisoning (serum iron 5270 μg/dl at 8 hours post-ingestion, and 20 900 μg/dl at 4 hours post-ingestion), who had elevated prothrombin times and elevated activated thromboplastin within 8 hours of ingestion. They point out that early coagulopathy has been seen in animal models during iron poisoning and in vitro when iron is added to human plasma. They believe that iron has a direct, reversible effect on enzymes of the coagulation cascade. In serious intoxications, patients may also present with shock, lethargy, and coma during this phase.

– During the second phase of iron poisoning (6–12 hours post ingestion), referred to as the latency or quiescent phase, the patient appears to recover. Iron is being taken up by the target tissues but has not yet induced free-radical mediated injury. Some toxicologists question the existence of this phase, noting that subtle signs and symptoms of toxicity such as metabolic acidosis, poor peripheral perfusion, oliguria, and lethargy are often present but missed [22]. Many patients recover completely after the first phase.

– Those patients progressing to the third phase of iron poisoning (12–48 hours post ingestion) develop shock and metabolic acidosis. Shock is the most common cause of death and its causes are multifactorial. Early shock (during phase one of iron poisoning) is hypovolemic, and is caused by early gastrointestinal fluid and blood loss. Within 8–48 hours there is loss of arteriolar tone and increased capillary leakage resulting in distributive shock. This form of shock may be caused by iron's direct action on blood vessels or by release of vasoactive substances such as serotonin, histamine, or ferritin. During this time the patients will have hemoconcentration, increased systemic vascular resistance, tachycardia, decreased central venous pressure, and peripheral cyanosis. At 2–3 days post ingestion there may also be evidence of cardiogenic shock, typified by increasing central venous pressure and decreased cardiac output. This last phase was well described in three patients who died from shock 1–5 days after iron intoxication, despite aggressive fluid and inotropic support. All three patients had stainable iron in their myocardium and evidence of contraction band necrosis and myocytolysis upon microscopic evaluation [23]. It is likely that as iron is deposited in the myocardium there is delayed onset of myocardial tissue destruction, eventually resulting in loss of cardiac contractility.

Metabolic acidosis with an elevated anion gap commonly accompanies shock during the third phase. Hypoperfusion with a concomitant shift from aerobic to anaerobic metabolism and subsequent build-up of lactic acid is an important etiology for this metabolic acidosis. Significant hydrogen ion formation may also accompany the conversion of ferrous to ferric iron and its subsequent reaction with water to form ferric hydroxides as shown below:

$$Fe^{+2} \rightarrow Fe^{+3} + H^{+}$$
$$Fe^{+3} + 3\ H_2O \rightarrow Fe(OH)_3 + 3H^{+}$$

By peroxidizing the lipid membranes of mitochondria, iron may physically disrupt the electron transport system located in their cristae, again interfering with aerobic metabolism. It is also possible that iron may pull electrons from the electron transport system as ferrous iron is oxidized to the ferric state in the presence of mitochondrial oxygen [24].

– **The fourth phase of iron poisoning** occurs at 48–96 hours post ingestion and is characterized by hepatic failure. It may be superimposed on the third phase. Damage is usually localized to the periportal areas of the liver. In some patients full hepatic failure occurs, making this complication the second most common cause of death during iron poisoning. Complications of liver failure include hypoglycemia, coagulopathy (depressed activity of factors V, VII, IX, and X without thrombocytopenia), cerebral edema, hyperammonemia, sepsis, and pancreatitis. Renal failure is a rare manifestation during this phase, but has been reported [25].

– **The fifth phase of iron poisoning** consists of gastric outlet obstruction occurring 2–5 weeks post ingestion. Gastric or pyloric strictures are most common.

Assessment

The assessment of an iron-poisoned patient is based on the dose ingested, clinical presentation, and laboratory results. All patients who are symptomatic (vomiting, diarrhea, lethargy) or have ingested >40 mg/kg of elemental iron are sent to the nearest emergency department. Upon arrival the patient is evaluated for signs of blood loss (CBC with hematocrit and hemoglobin) metabolic acidosis (arterial blood gases and serum electrolytes), and shock (orthostatic blood pressure monitoring).

The laboratory assessment of iron-poisoned patients has changed recently due to mounting evidence that standard tests were not as valuable as once thought. The standard work-up for an iron poisoning used to include a serum iron drawn 4–6 hours post ingestion along with a total iron binding capacity (TIBC). If the serum iron exceeded the TIBC the patient was considered to be at risk for developing toxicity since free iron was available to injure target organs. As a result, the patient would be started on antidotal therapy. Several investigators have shown that the TIBC will become falsely elevated during iron poisonings due to laboratory aberration [26–28]. Thus, the TIBC is no longer recommended as a criterion for initiation of deferoxamine therapy. Instead there is a greater reliance upon a peak serum iron concentration, the patient's clinical condition and/or results of a deferoxamine challenge test.

Peak serum iron specimens should be drawn 4–6 hours post ingestion for non-sustained release preparations and 6–8 hours post ingestion for sustained release preparations. Ideally, specimens should be drawn before the patient is

started on deferoxamine therapy since ferrioxamine will falsely lower the serum iron values obtained by the chromogenic methods used by most hospital laboratories [29]. Serial determinations should be considered in symptomatic patients, in large ingestions, or in cases where sustained release preparations have been ingested. Serum iron concentrations normalize quickly once iron distributes from the central compartment, so greater reliance should be placed on the patient's clinical state after four hours post ingestion.

There is a crude correlation between peak serum iron concentration and outcome. In Westlin's experience with 172 iron poisoned children, the incidence of coma and shock was 8% among children with initial serum iron concentrations of less than 500 μg/dl. It rose to 37% in those with serum iron concentrations of 500 μg/dl or greater and to 70% in the group with serum iron concentrations of 1000 μg/dl [30]. The highest survived serum iron concentration was 16,706 μg/dl [31].

The white blood cell count and blood glucose have been advocated as a quick screening tools for possible acute hyperferremia when serum iron testing was not available. In a retrospective study of 138 patients presenting with acute iron poisoning, elevated white blood cell counts (>15 000 mm^3) and elevated blood glucose values (>150 mg/dl) showed positive predictive values for patients having a serum iron >300 μg/dl [32]. Two recent analyses using the same inclusion criteria have not been able to duplicate this observation [33,34].

Abdominal radiographs are useful for the assessment of decontamination procedures and should be performed during suspected poisoning involving prenatal strength tablets or capsules. The radiopacity of iron diminishes with its concentration, so X-rays are less likely to be useful for children's chewable strength preparations (15–18 mg elemental iron per tablet), liquid iron preparations, and after tablets or capsules have dissolved.

Other useful ancillary tests for admitted patients include guaiac of stool and gastric aspirate, coagulation studies, blood type and cross match, liver function and renal function tests.

A deferoxamine challenge is useful when serum iron testing is not available or when a patient's serum iron concentration is borderline toxic (350–400 μg/dl). The test is performed by administering 90 mg/kg deferoxamine intramuscularly, up to 1 g in children or 2 g in adults. The presence of vin-rosé (pink) colored urine within 2 to 3 hours signals that free iron in present and that further chelation should be performed.

Treatment

Treatment of the iron-poisoned patient consists of providing supportive care, preventing further absorption of iron, and chelating free iron with deferoxamine. On rare occasions, methods to enhance elimination of iron via exchange transfusion are considered. There have been no controlled human clinical trials comparing treatment protocols and so there is considerable controversy regarding optimal therapeutic interventions.

Supportive care. Patients requiring hospital evaluation should be exam-

ined carefully for evidence of early signs of shock and metabolic acidosis. Usually this will involve assessment of vital signs, evaluation for orthostatic blood pressure changes, and scrutiny of laboratory tests. Patients showing signs and symptoms of iron intoxication (acidosis, hypotension, lethargy, tachycardia) should be admitted to an intensive care unit where continuous monitoring of vital signs and peripheral perfusion may be accomplished. Shock may be treated with crystalloid volume replacement (lactated ringers or normal saline) and/or whole blood depending on the patient's blood loss. Acidosis may be treated with IV sodium bicarbonate. Swan–Ganz monitoring is essential for all patients developing shock since it is the primary cause of death and since its character changes with time. Swan-Ganz monitoring allows the clinician to recognize when the patient has moved from hypovolemic and distributive shock into cardiogenic shock. At this point treatment changes from volume replacement and inotropic support (i.e. dopamine) to inotropic support with afterload reduction (i.e. nitroprusside). Although the change in treatment may seem subtle, from our experience this is a critical step in maintaining patient viability.

As the patient enters liver and renal failure, dialysis and clotting factor replacement become important. Liver transplant has not been attempted to date in this setting.

Preventing absorption. Once the patient has been stabilized an attempt should be made to remove residual iron from the gastrointestinal tract. We prefer using whole bowel irrigation for solid preparations and gastric lavage for liquid preparations. Whole bowel irrigation has been shown to be both a safe and effective method for removal of poisons from the gastrointestinal tract and is ideally suited for removal of poisons that are not adsorbed to activated charcoal, such as iron [35,36]. There has been abundant experience with whole bowel irrigation during iron poisonings. Patients have ranged in age from 11 months to adulthood. In seven cases whole bowel irrigation retrieved iron tablets that lavage with a large-bore orogastric tube or ipecac-induced emesis failed to remove [37–39]. In one instance the procedure was used without complication in an 18-year-old pregnant female who overdosed with iron at 38 weeks of gestation. The patient delivered a 3550-g female infant without perinatal complications five weeks later [40].

Whole bowel irrigation involves administering a commercially available isotonic, balanced electrolyte solution (e.g. Golytely®, Colovage®, OCL®, CoLyte®) containing polyethylene glycol, at a rate that exceeds the intestinal absorptive capacity. The result is mechanical cleansing of the gastrointestinal tract. In toddlers the rate of administration is 0.5 l/hr while in adolescents and adults 2 l/hr is standard. Insertion of a nasogastric tube is often required in younger patients. Ipecac should not be administered prior to the whole bowel irrigation since persistent vomiting impedes the procedure. If vomiting occurs during administration the infusion rate should be temporarily slowed with a return to the normal infusion rate as soon as possible. Intravenous metoclopramide (0.1–0.3 mg/kg in children and 10 mg in adults) has been used because

of its antiemetic properties and its ability to hasten upper gastrointestinal transit time. Administration should continue until the rectal effluent is clear, often requiring 4–6 hours of irrigation. Water retention and electrolyte disturbances are theoretical adverse effects. They have not been reported when commercially available bowel irrigant solutions are used. More frequently patients complain of nausea, abdominal fullness and bloating. Whole bowel irrigation should not be used for patients who are becoming obtunded, or in those presenting with evidence of gastrointestinal hemorrhage, obstruction or ileus [41].

Emesis with syrup of ipecac may be used as an alternative to whole bowel irrigation, provided the patient has no evidence of central nervous system depression or active gastric bleeding. Orogastric lavage with a large bore tube is a suitable option especially for liquid preparations. It may be used for iron containing tablets and capsules provided they fit through the opening of the lavage tube.

A repeat abdominal X-ray should be obtained after the gastrointestinal decontamination procedure to verify expulsion of the iron preparation.

Activated charcoal does not bind iron appreciably [42], so attempts have been made either to convert intragastric iron into an insoluble salt or to complex the iron with deferoxamine in order to de-activate it. At present there are no data substantiating the therapeutic benefit of oral complexation of iron during an overdose. The medical literature is replete with reports of patients suffering adverse effects secondary to oral complexation of iron.

Orally administered sodium bicarbonate or sodium dihydrogen phosphate solutions were advocated for conversion of iron to insoluble ferrous carbonate and ferrous phosphate salts respectively. An *in vitro* study by Czajka et al. [43] showed that only 17% of iron was complexed when 0.1 M iron was combined with 1 M bicarbonate. Only 6% of the iron was complexed when dihydrogen phosphate was used at the same concentration. These were the best complexation rates attainable in their studies. Such rates would not be expected during overdoses where the molar ratio of iron to complexor would be much higher. *In vivo* studies by Dean et al. [44,45] have corroborated Czajka's work, showing that complexation with bicarbonate or phosphate were of no value in preventing iron absorption when used in simulated overdoses in rat and pig models.

Perhaps more disturbing are the reports of toxicity associated with the use of dihydrogen phosphate for oral complexation of iron. Life-threatening hyperphosphatemia, hypocalcemia, and hypernatremia have accompanied administration of disodium phosphate enemas when given to children for oral complexation of iron [46,47]. Hypernatremia and metabolic alkalosis would be possible side effects of sodium bicarbonate therapy, but have not been reported at this time.

For many years, antacids have been known to inhibit iron absorption during therapeutic dosing [48,49]. Corby et al. [50] have suggested using magnesium hydroxide containing antacids to prevent absorption of iron by converting it to insoluble iron hydroxide salts. In a dog model they demonstrated that doses of magnesium hydroxide that were 5–10 times greater than the dose of elemental iron would significantly inhibit iron absorption and would prevent early signs

of toxicity. Clinically insignificant hypermagnesemia was observed in all dogs receiving the magnesium hydroxide. There is no published experience with this treatment's efficacy in humans. Clinically significant (hypothermia, coma) hypermagnesemia has been reported after ingestion of 200 g of magnesium sulfate (1600 mEq Mg^{+2}) in a 25-year-old female with normal renal function [51]. Conceivably a patient being treated for an ingestion of 4.5 g of elemental iron might receive the same magnesium load if 10 g of magnesium hydroxide were used to complex 1 g of elemental iron.

Oral complexation with deferoxamine has also been recommended. Support for this treatment is based on *in vivo* work conducted by Moeschlin and Schnider [52]. They enhanced the survival rate of guinea pigs to 60% when an oral lethal dose of iron was followed 30 minutes later by an equimolar dose of oral deferoxamine. Serum and urinary iron monitoring were not performed so it is unclear whether deferoxamine actually prevented absorption of iron.

Data from animal experiments conducted by Witten et al. [53] indicate that the complexed iron, ferrioxamine, is absorbable and is toxic. When four mongrel dogs were given a lethal dose of iron mixed with an equimolar amount of deferoxamine, all had measurable ferrioxamine in their serum and showed signs of iron poisoning. All four animals died. In a later study [54], Witten's group orally administered a lethal dose of elemental iron in the form of ferrioxamine to five mongrel dogs. Three animals developed significant hypotension and two animals died, presumably from the toxic effects of ferrioxamine. No ferrioxamine blood monitoring was performed in this study.

Numerous patients have been treated over the past two decades with various regimens of oral plus parenteral deferoxamine, but no controlled studies have examined the therapeutic efficacy of this strategy until recently. In a cross-over study using human volunteers, seven subjects were given 5 mg/kg elemental iron orally. Serial iron levels were measured using a spectrophotometric technique and areas under the curve were used to determine iron absorption. In the second phase the same procedure was used but the patients received an equimolar dose of deferoxamine with their iron. There was no significant difference in the areas under the curve for both phases of the study indicating that iron absorption was not impaired by oral deferoxamine [55].

Gastrotomy should be considered for the removal of tablets that become adherent to the gastric mucosa or for removal of iron concretions. Such an occurrence is confirmed by pre- and post-decontamination radiographs in multiple planes [56–58].

Deferoxamine therapy. The antidote for iron poisoning is deferoxamine. Deferoxamine is a water soluble compound with a molecular weight of 597 daltons. It has a high affinity for ferric iron, forming a stable octahedral iron complex known as ferrioxamine. One mole of deferoxamine binds one mole of ferric iron. Theoretically, therefore, 100 mg of deferoxamine binds 9.35 mg of Fe^{+3}. Complex formation is affected by pH, with a greater portion of the stable ferric complex being formed at pH > 6 [53]. Deferoxamine does not appreciably bind other physiologic metals such as copper, magnesium, zinc and calcium. It

does have an affinity for aluminum and has been used for treatment of aluminum toxicity in chronic renal failure.

Deferoxamine chelates free iron and possibly iron in transit between transferrin and ferritin. The chelated iron is then rapidly excreted unchanged into the urine. Deferoxamine's action is dependent on both its ability to enhance iron elimination and on its ability to affect iron distribution. The volume of distribution of ferrioxamine is considerably smaller than that of deferoxamine (Vd of deferoxamine = 60% body weight; Vd of ferrioxamine = 20% body weight) so once iron is chelated it may be sequestered away from target organ mitochondria and into the extracellular fluid where elimination can begin [10].

Deferoxamine is indicated for patients showing signs of serious intoxication (shock, metabolic acidosis, coma), for patients with serum iron concentrations ≥350 μg/dl (62.6 μmole/l), or for patients with a positive deferoxamine challenge test. We prefer administering deferoxamine intravenously at 15 mg/kg/hr up to 6 g/day, however it may also be given intramuscularly (90 mg/kg up to 1 g/dose every 8 hours).

Hypotension was associated with early intravenous bolus dosing of deferoxamine at rates four times faster than the currently recommended regimen [10]. Westlin [30] recommended the current rate of infusion after publishing the results of a cooperative study involving 172 children treated with deferoxamine. Four of the patients developed tachycardia and hypotension during deferoxamine infusion. In each case the deferoxamine was being administered by rapid infusion. Higher rates (up to 35 mg/kg/hr) have been used with no apparent side effects and may be required for life-threatening iron intoxication [31,59].

The endpoint of deferoxamine therapy has traditionally been marked by a return in urine color from vin-rosé to amber-yellow. This change is dependent on the concentration of ferrioxamine in the patient's urine and may be imperceptible even to the most discriminating clinicians. Serum iron concentrations cannot be solely relied upon as an endpoint for antidote therapy because they may be normal while the patient is in the third phase of iron poisoning. Clinical improvement is a helpful marker and many physicians will continue deferoxamine therapy for 6–12 hours after the patient has shown signs of improvement. If the patient is entering the latency phase however, there is a chance that the deferoxamine could be discontinued prematurely.

Yatscoff et al. [60] have developed objective criteria for discontinuing deferoxamine therapy that depend on determining the urinary iron to creatinine ratio. A ratio of >12.5 indicates that chelatable iron is still present and that deferoxamine should be continued. The method involves releasing iron from urinary ferrioxamine using a reagent comprised of 2% v/v thioglycolic acid plus 10% v/v trichloroacetic acid. This method shows promise if hospital laboratories are willing to provide the test routinely.

Side effects related to short-term deferoxamine administration include hypotension (already discussed), fever, dysuria, leg cramps, rashes, and puritis. Intramuscular injection may cause local pain and erythema. Transient renal insufficiency has rarely been associated with intravenous deferoxamine use.

Renal function returned to normal once the infusion was stopped [61].

A more recently appreciated adverse effect of deferoxamine is its pulmonary toxicity. Tenenbein et al. [62] described four patients who developed fatal lung injury after being treated with continuous infusion deferoxamine (15 mg/kg/hr) for acute overdose of iron. The pulmonary injury met clinical and pathological criteria for acute respiratory distress syndrome (ARDS) and had an onset of 32–72 hours. All of the patients were young adults and had no risk factors for lung injury. In reviewing their hospital's experience with continuous infusions of deferoxamine in acute iron intoxication, they noted that no patients developed pulmonary complications when treated for 24 hours or less, and recommended that deferoxamine infusions be limited to 24 hours in duration. The injury has been reproduced in a mouse model and is attributed to free radical mediated alveolar damage [63]. A similar syndrome has been described in other acute iron overdose patients treated with continuous infusion deferoxamine [64] as well as in patients treated for chronic iron overload or advanced cancers with continuous infusion deferoxamine [65–67]. Until more is known about this adverse effect it would be reasonable to attempt to limit continuous infusion deferoxamine to less than 24–36 hours and to consider high dose intermittent infusions when prolonged chelation is likely. Chelation should be stopped at the first signs of pulmonary toxicity.

Enhancing elimination. Extracorporeal measures for enhancing the elimination of iron, such as hemodialysis, play a very limited role in the treatment of this poisoning. Iron distributes too rapidly to peripheral tissue to utilize hemodialysis as a means of enhancing its elimination. Exchange transfusions have been advocated for recent serious exposures (serum iron >1000 μg/d and clinical deterioration despite deferoxamine) [68], based on studies conducted in mongrel dogs that indicated that mean iron clearance by exchange transfusion was 30 times greater than by deferoxamine chelation [69]. However, the total iron removed by each exchange averaged 12.7 mg elemental iron or only 0.8% of the total dose administered. Ideally these exchanges should be made before shock and acidosis occur in order minimize blood pressure fluctuations. Hemodialysis would be indicated for removal of ferrioxamine in patients with renal impairment being treated with deferoxamine.

In conclusion, even though the mortality associated with iron poisoning has decreased precipitously from 50% in the 1950s to less than 1% in the 1990s, iron is still a major cause of poisoning death in the pediatric population. High molecular weight conjugates of deferoxamine, new oral hydroxypridone chelators, and antioxidant therapies all show promise for reducing the fatality rate even further [70,71]. Until these improved treatments become available clinicians, parents and industry must share responsibility in preventing this poisoning. Obstetricians and gynecologists must counsel their maternity patients about the dangers posed by accidental poisoning in children from prenatal iron. Parents must learn to keep these products in child-resistant containers in a locked cabinet. Industry must repackage, reformulate, and relabel iron supplements to make them safer for consumers and their children.

IMIDAZOLINE CONTAINING OTCs

Imidazoline decongestants were introduced in 1942 and since that time various formulations have become widely used and readily available in numerous OTC preparations. The imidazoline preparations include naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline [72]. Oral ingestion and topical applications can rapidly produce toxicity. Most of these drugs are composed of an aromatic nucleus plus a side radical containing an NH or NH_2 group which are called pressor amines and are used for nasal and ophthalmic decongestion and vasoconstriction. These drugs act on α_1 and α_2 adrenergic receptors. When applied therapeutically to the cornea or on nasal passages, α_1 adrenergic stimulation predominates. When ingested, central α_2 adrenergic receptor stimulation predominates. Chronic dependence can occur in adults using naphazoline nose drops for long periods of time producing chronic nasal congestion, which resolves when the medication is discontinued. This effect is a rebound phenomenon. Oral ingestion and topical misuse can both produce toxicity.

Waring [73] reported in 1945 for the first time in the United States sedation in three children using a naphazoline nasal solution. These three cases developed drowsiness after 5 drops of a 0.1% solution of naphazoline, 2 drops of a 0.05% solution, and the third case of 7–8 cc oral ingestion of a 0.05% solution. Since these early reports, numerous cases of toxicity have been reported [74–79]. Usually initial excitement is followed by 1.5 to 2 hours of somnolence, lethargy, and bradycardia.

Ocular preparations are a common OTC used for vasoconstriction and decongestant effects. Tetrahydrozoline is the most commonly used OTC in the US. It is effective and safe when applied to the eye according to directions. When ingested in a small amount, it can result in severe central nervous system depression. The most recent review by Klein-Schwartz et al. [80] reported on two cases of prolonged central nervous system depression due to accidental ingestion. Case one, a 20-month-old, ingested 15 ml of tetrahydrozoline-containing eyedrops. During the following five hours drowsiness increased and the patient became fussy, irritable, flushed with dry skin, and had a pulse of 150. During the hospital stay the child was carefully monitored and 20 hours later was normal. Case two involved a 2-year-old who ingested 7.5 ml. Four hours later the child was obtunded, responding only to painful stimuli. Vital signs were normal and the second day the child was normal. A review of phone calls to the Maryland Poison Control Center showed that 89.1% were children under 2 years. Twenty-six of 59 ingestions were treated with an emetic; twenty-four with syrup of ipecac, one with salt water and one with gagging. Seven patients developed symptoms and one was hospitalized. The salient feature of the toxic response is different. The expected symptoms would be elevated blood pressure, tachycardia, and headache in adults. But children show CNS depression which can range from drowsiness to coma, but can alternate with periods of hyperactivity and agitation. Bradycardia, hypoten-

sion, with vasomotor collapse can also occur. Resolution on symptoms usually occurs in 24 hours.

The imidazolines have no specific antidote. Treatment is activated charcoal to prevent further absorption plus supportive care. Syrup of ipecac should not be used since there may be rapid onset of central nervous system depression.

LOPERAMIDE

Consumers may purchase a wide variety of agents to subdue diarrhea including, attapulgite, polycarbophil, bismuth subsalicylate, kaolin and pectin, loperamide, and diphenoxylate plus atropine. Diphenoxylate plus atropine has a well-founded reputation for causing serious poisoning in pediatric patients, but is not yet available over-the-counter in many countries including the United States (see Chapter 9).

Loperamide, an over-the-counter antidiarrheal, is available throughout the world and is sold under various trade names, e.g. Imodium®, Lopemid®, Loperin®, Loperyl®, etc. It is available as 2 mg capsules, 2 mg caplets, and as a cherry-flavored liquid (1 mg/5 ml). Loperamide is currently indicated in the United States for control of symptoms associated with acute nonspecific diarrhea, however, it has also been used for symptom control during chronic diarrhea secondary to inflammatory bowel disease and gastric surgery.

Loperamide has a number of advantages compared to conventional antidiarrheals. Controlled clinical trials in adults have shown that loperamide has a more rapid onset of effect, a longer duration of action, and imparts superior stool control compared to diphenoxylate, attupulgite, bismuth subsalicylate, clioquinol, and kaolin [81]. Even though loperamide is 2–3 times as potent as diphenoxylate on a milligram per milligram basis, it has no apparent central nervous system opioid effects in adult patients, and consequently has a lower potential for psychological abuse than diphenoxylate. Loperamide rarely produces side effects and those that occur are usually minor (rashes, gastrointestinal complaints that may have been caused by the pre-existing condition). Finally, many patients prefer loperamide because it may be taken in doses once or twice a day and is conveniently packaged.

Loperamide is a congener of meperidine. It acts by enhancing the contraction of the circular muscle of the jejunum through opioid receptors thereby inhibiting peristaltic activity. It may also have anti-secretory activity and may interact directly with cholinergic and non-cholinergic nerves lining the gastrointestinal wall.

The recommended dose for adults is 4 mg followed by 2 mg after each unformed stool, not to exceed 16 mg per day. Approved dosing regimens in the pediatric population have varied from country to country. In the United States loperamide is not recommended in children under two years of age, while in the United Kingdom it is not approved for use in children less than 4 years of age. In developing countries the lower age limit is reduced to one year. Typically,

pediatric patients are dosed in the range of 0.08–0.24 mg/kg/day divided into two to three doses.

In therapeutic doses it is likely that only a small portion of loperamide is absorbed systemically. Radiolabel studies in rats show that most of the drug becomes bound to the intestinal lumen (85%), presumably to opioid receptors [82]. In humans, peak plasma levels occur at four hours post ingestion and account for only 0.3% of administered dose. The small amount of drug that does get absorbed is nearly completely bound to plasma protein (97%) [83]. In addition, there is significant first-pass metabolism of free drug to a glucuronide conjugate [81]. The greatest portion of eliminated drug is recovered in feces (40%) and urine (10%). The elimination half-life ranges from 7–15 hours [84]. During an overdose of loperamide it is likely that the absorption phase would be prolonged due to decreased peristaltic activity.

Although loperamide has been successfully used in the pediatric population [85], there is growing evidence to support increased susceptibility to loperamide toxicity in children under three years of age. Poisonings from loperamide have been noted after both acute and chronic use of the drug.

There have been at least nine reports in the medical literature of pediatric poisoning from loperamide involving a total population of thirty children [86-94]. All of the cases have involved children under four years of age. Two-thirds of the poisonings resulted from therapeutic misuse of OTC loperamide by parents, especially in developing countries. The remainder of the poisonings resulted from prescription loperamide.

Pediatric poisoning from loperamide has resulted from both acute and chronic dosing. A single dose of 0.045 mg/kg loperamide produced paralytic ileus in a one-year-old child lasting seven days [90]. A 15-month-old female was given a single 0.125 mg/kg dose of loperamide for treatment of diarrhea secondary to stress from burns to 35% of her body. She collapsed, became bradypneic, pale and unresponsive within 50 minutes of dosage administration [87]. The patient was resuscitated and given naloxone and recovered over the next 24 hours. Hypoalbuminemia, mildly impaired liver function, and prior damage to the intestinal wall may have enhanced the bioavailability of loperamide in this patient. In another 4-month-old patient without these prior medical conditions a single dose of 2 mg/kg produced coma, bradypnea, miosis, muscle rigidity and ashen color several hours after dose administration. This patient was also treated with multiple doses of naloxone and recovered over the next 24 hours.

Significant toxicity has also been associated with chronic dosing of loperamide in children under four years of age. Most often patients developed central nervous system depression, bradypnea, miosis when administered doses of 0.2 mg/kg/day or greater [92–94].Usually the drug was being administered every four to eight hours for treatment of toddler's diarrhea in patients with no prior history of liver impairment. The patients became progressively more obtunded on the second and third dose and would gradually recover with supportive care over the next 3 to 4 days. The smallest chronic dose to produce

noticeable toxicity was 0.1–0.12 m/kg/day. In this series a 23-month-old and two 34-month-old children developed irritability, drowsiness, personality changes, and "unacceptable behaviour" on days 3–5 of therapy [88]. Symptoms subsided within 48 hours of discontinuation of loperamide. The largest tolerated dose involved a child with short bowel syndrome who was gradually increased from 6 mg/day loperamide at 6 weeks of age to 18 mg/day at 4 months of age. The patient was administered 18 mg/day (4 mg/kg/day) for one week when he developed poor peripheral perfusion, miosis, hypothermia, and suffered a generalized convulsion. He made a full recovery with supportive care [91].

The death of six Pakistani children has been attributed to the therapeutic misuse of loperamide by the public [86]. This is the largest series reported to date and encompasses 19 children ranging in age from 1.5 months to 6.5 months plus a 2-year-old. All patients presented with abdominal distention and paralytic ileus and had been dosed with 0.4–2 mg/day. Malnutrition may have enhanced susceptibility to loperamide toxicity in this population by increasing bioavailability of the drug.

There has only been one report of overdose from loperamide in adults and it is unlikely that loperamide played a significant role in this patient's clinical course. The case involved a 28-year-old female who ingested 20 mg of loperamide, 3800 mg of flecainide acetate, 50 mg of diazepam and 100 g of ethanol. She developed polymorphous ventricular tachycardia approximately two hours after ingestion. She had prolonged electrocardiographic time intervals which decreased with normalization of serum flecainide concentrations [95].

From these reports it would appear that loperamide may produce significant toxicity (respiratory depression) in single doses as low as 0.1 mg/kg and in chronic dosing of 0.1 mg/kg/day or greater in children less than four years of age.

Loperamide poisoning should be suspected in any patient presenting with miosis, central nervous system depression including bradypnea, and/or paralytic ileus. Serum and urine assays for loperamide are not readily available so diagnosis is usually dependent on clinical impression, history, and reversal of symptoms with naloxone.

Treatment of loperamide poisoning initially consists in stabilizing the patient's vital signs. This may be accomplished by providing respiratory assistance or by reversing the respiratory depression using naloxone (children: 0.01–0.1 mg/kg iv; adults: 0.4–1 mg iv). Since loperamide has a longer duration of action than naloxone, intermittent dosing may be required. Continuous infusions of naloxone have not been used with overdoses of loperamide but would be worthy of consideration. Longer acting opioid antagonists such as nalmefene may also be beneficial once there is more experience with them and they become available.

Once the patient is stabilized single doses of activated charcoal should be administered to prevent further absorption of loperamide. In large recent ingestions lavage with a large-bore orogastric tube may also be indicated. Small recent ingestions (0.05 mg/kg) may be managed at home with syrup of ipecac and close follow-up. Efforts to enhance the elimination of loperamide via

invasive techniques such as dialysis, hemoperfusion, and forced diuresis will not be helpful since most of the drug that is absorbed is highly protein bound. Enhancement of loperamide via non-invasive strategies (multiple dose charcoal) is also not recommended since there is no evidence that loperamide is enterohepatically or enteroenterically recycled in humans and because there is high probability that multiple doses of charcoal in this setting may cause impaction.

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18. Substances of abuse

The history of substances of abuse is as old as mankind itself. Whenever pain, suffering, sorrow, grievance, hunger, misery, injustice, despair, illness or misery have afflicted man, he has tried to find ways to relieve his problems. For as long as we can go back in history, natural or artificial substances were being used for that purpose. As time went by, some of these behaviours became integrated as part of the religious, social or therapeutic rites of different societies. Others were rejected, being considered antisocial, immoral, illegal or dangerous. From time immemorial until now, it has been impossible to clearly separate the use of chemicals, drugs, plants, mushrooms or even food to modify our perception of our environment, our mood, our feelings, our physical sensations, our perception of pain, our perception of suffering or joy from a whole range of our values; social, cultural, political, legal, religious, moral, familial or individual.

Reading the scientific and lay press of the last decades would convince anyone that all these factors are closely related and that the frontier lines between all those aspects of our societies are too difficult to be drawn. This may even be felt when the scientific literature on substances of abuse is being reviewed. Interestingly, this area of scientific and medical research can be compared with the evolution of knowledge and opinions in the area of infectious diseases. In the last centuries, some infectious diseases like leprosy or even tuberculosis were associated with social rejection. However, during the last decades, these prejudices have seemed to disappear and scientific research in the areas of microbiology, epidemiology, pharmacology and public health have appeared to work together to decrease the threat of infections and epidemics. Only recently, the appearance of AIDS has apparently woken old devils, especially because the epidemic started in homosexuals and communities of drug addicts. Some public health officers in North America were even heard promoting the creation of special camps to put these patients in quarantine.

In the area of substances of abuse, subjective factors have always been present. The involvement of the medical profession in the research, treatment or prevention of this problem has always been coloured by the perception that each professional may have of the causes, the moral and social impacts of the disease, the financial, political and legal aspects of the problem, the relative

importance of genetic, biological, psychological or social factors and his specific role in this context. At this point, I would like to cite a nice description of the way the medical profession got progressively involved in this area from the end of the 19th century to the present day: *"In those years, and in the first quarter of this century, there was a gradual change in the way that drug taking was perceived. An important factor in this was the rise of the medical profession. One way in which it sought power was to give everything possible a medical diagnosis, thereby staking a claim on that part of human activity. For example, in the United Kingdom manifest wickedness became psychopathy. It was agreed that it did not respond to treatment, but special hospitals were built in which doctors could manage those suffering from it. There was little recognition of the wretched lives lived by those at the bottom of society; it was much easier to describe them as addicts and then try to devise a treatment to 'cure' them. We still do it. The disadvantaged blacks and Hispanics in the United States destroy themselves with cocaine and its derivatives, and our Aborigines do the same with alcohol and petrol."*.

There is more political acclaim to be gained if one billion dollars are spent in "the war against drugs" than in ameliorating the world in which the poor live [1]. This affirmation may still be observed in the United States where illicit drugs have developed to such a level of gravity during the last three decades that the President has had to declare the country at war with drug producers, dealers and users. However, the problem was perceived not as a public health threat but as a fight between law and crime. This is clearly illustrated by the budgets allocated to each sector: In 1990, nearly 40% of $8.8 billion went to law-enforcement efforts, 20% to building correctional facilities, 15% to the development of new prevention and education programs, and less than 12% to improving the quality and capacity of drug abuse treatment [2].

Another good example of the prime importance of all these factors for the perception and management of use and abuse of even the so-called legal drugs is cigarette smoking. Only twenty years ago, when some of us tried to implement anti-smoking programs, the vast majority of people considered us to be lunatics, day-dreamers or even individuals disrespectful of other people's liberty. Nowadays the situation is totally reversed, at least in North America. Most, if not all, public buildings are smoke-free. The same policy applies to all continental and many intercontinental flights. Compulsory advice can be read on cigarette packages, for example "*Surgeon General's Warning: Smoking causes lung cancer, heart disease, emphysema and may complicate pregnancy*". From a simple and socially accepted bad habit, cigarette smoking has become, in only a few years, an addiction which should be prohibited as much as possible [3].

CURRENT ISSUES AND RECENT STUDIES

Even if the subjective difficulties of the study and management of substances of abuse are disregarded, many practical difficulties should still be dealt with:

- Animal data is difficult to extrapolate to the human complex reality.
- A precise history of the consumption of frequently illicit drugs is difficult to obtain and both clinicians and researchers have to rely largely on questionnaires.
- Proper analytical facilities which could provide confirmation of drug-taking histories are seldom available.
- Single drug abuse is not the rule.
- Multidrug use along with over-the-counter and prescription drugs, tobacco and alcohol is frequent.
- Low socio-economic status, poor health, malnourishment, infectious diseases including AIDS, psychological or psychiatric problems, social and familial conflicts may be both causative factors and consequences of drug abuse.
- Due to the lack of standardization in terminology, the classification of substances, disease or outcome definitions, comparisons between animal and human studies are difficult. National and international organizations have tried to circumvent these problems by reaching consensus on different aspects of the semantic and technical approaches, with variable success [4]. Terms like *"addiction"*, *"habituation"*, *"dependence"*, *abuse"*, *"misuse"*, *"withdrawal syndrome"*, are still used with different connotations in the medical literature. Once again, this impedes our capacity to compare studies especially if they are not contemporary and originate from different countries.
- Another difficulty is related to the fact that drugs used in the streets are not well-defined products but instead are unknown mixtures of active ingredients, additives, diluents, adulterants and impurities [5]. The clinical evaluation of patients and the measurement of the efficacy of treatment protocols are therefore more complex.

Lack of standardized definitions

Even the definitions of terms and their interpretation may be conflictual. An interesting and amusing description of the addictive personality as it applies to a scientist appeared in an editorial of *Science* [6]: *"An addictive person is one who has a compulsion to behave in ways that his or her family members consider detrimental to their interest. An addictive person will frequently conceal the extent of his addiction, will lie to his family about it, is immune to logical arguments to correct the error of his ways, and foregoes income that would require abandoning the addiction.*

– Science: *Are you talking about dope addict or alcoholic ?*

– Dr Noitall: *No, I am describing a scientist. It is well known that work habits of scientists are addictive, leaving their spouses in tears, their children pleading "Come home, mummy (or daddy)", and involve long hours in hostile instrument laboratories or cold rooms, exposed to noxious gases and radioactivity — conditions that no sane person would choose."*

This definition may also very well apply to many businessmen or professionals who suffer from work alcoholism.

The conflict between those who consider addiction as a pure organic disease and those who consider that it is strictly a behavioural problem is far from over. It influences not only research orientations but also the global approach to "patients" or "victims". The importance of genetic factors in the etiology of addiction is still a strongly debated subject [7,8]. Even though a multidisciplinary approach is widely claimed to be essential when dealing with substances of abuse, the area of training and expertise of different authors is frequently obvious when reading their discussion and conclusions.

These constraints are easily perceived in surveys on substances of abuse around the world. Conflicting results are not exceptional since databanks are not using standardized criteria for the definition of cases, interventions or outcome [9–17]. Many surveys have concentrated on specific at-risk populations like the Indians in North America [18–21]. They are good examples of the importance of social, cultural, economic and political factors. In some of these minorities, drug abuse may even be used as a symbol of the rejection of authorities or an expression of total distress. Group suicide by solvent inhalation in Inuit youngsters of Baffin Island represents a good illustration of this alienation feeling. The period of adolescence with its emotional instability, insecurity, search of self-image, rejection of authority, need for peer acceptance, typifies a situation of high risk for the development of abuse behaviour in most societies [22–28].

Along with cigarette smoking, the definition of substances of abuse is progressively generalized to licit drugs including alcohol and prescription or non-prescription drugs. A few decades ago, narcotics and barbiturates were the main sources of either medical or non-medical drug overuse and abuse. In fact, a large proportion of pharmaceutical research in the past thirty years has been aimed at the development of effective but non-addictive analgesics and sedo-hypnotics. Every time a new drug was introduced on the market, it was claimed to retain therapeutic efficacy without the risks for tolerance and dependence. Among narcotics, we may remember the historical profiles of methadone, levallorphan, meperidine, propoxyphene, oxycodone, nalorphine and pentazocine. The same is true for the various sedative and hypnotic drugs developed to replace the "dangerous" barbiturates: glutethimide, methyprylon, meprobamate, methaqualone, chloral hydrate, ethchlorvynol, chlordiazepoxyde then all the other benzodiazepines. A large proportion of these drugs were later found to be as toxic or addictive as those they supposedly superseded. Some have been withdrawn from the market or added to the list of controlled drugs or their therapeutic indications have been changed. Surveys on their trends of abuse are still the subject of publications [29–33].

Recent concern over specific groups at risk

Pregnant women. Women and especially pregnant women have been the subject of much concern and studies [29–33]. All categories of substances of

abuse have been studied at one time or another. Cigarette smoking, alcohol intake, prescription and non-prescription drugs and finally, street drugs were evaluated for their impact on the evolution and outcome of pregnancies and also on the health and future development of the newborn. Discrepancies between studies are not surprising when the numerous confounding variables involved are considered.

Professions at risk. Studies have focused on the importance of profession in the risk of developing drug addiction. Doctors, pharmacists, nurses and veterinarians were considered by some authors to be at high risk because of an easy access to controlled drugs. However, many other factors like stress at work and reluctance to admit one's own problems and search for help seem to be of major importance [40–42].

Sport. Sport in the context of amateur competitions and even the Olympic Games is not free of drug abuse. Doping has become a major issue especially since the early 70's with an almost generalized abuse of anabolic steroids in some categories of competition (weight-lifting, weight-throwing, short distance swimming and racing). This phenomenon peaked with the disqualification of Ben Johnson after the Olympic Games of Seoul in 1988. The problem however is not limited to international champions. Professional sport is severely affected. Body builders and also youngsters trying to improve performance or body image are also frequent abusers [23,30,43].

Consequences and management of drug abuse

Medical, psychological and social complications of substance abuse have been a matter of concern ever since the first descriptions of alcohol, cannabis, tobacco or opium overuse in the pre-Christian era [1,44–50]. The intravenous use of drugs has been a major contributor to the medical complications of substances of abuse. Adulterants have led to the risk of introducing foreign particles in the bloodstream with consequent damage to the vascular system, the heart, the lungs, the brain or other organs. Major infections, such as endocarditis, pulmonary septic emboli, thrombophlebitis and osteomyelitis, have occurred. With the AIDS epidemics, sharing the needle became an important factor in the spread of the disease. A significant change in the pattern of abuse with drugs like cocaine, crack, phencyclidine, heroin and amphetamine derivatives significantly increased the occurrence of major complications like myocardial infarctions, cerebral infarctions and haemorrhages, convulsions, dysrhythmias, rhabdomyolysis and renal failure. Psychiatric complications such as depression, organic psychosis, severe emotional and behavioral disturbances, aggressiveness and suicide are both consequences and co-morbidity factors of drug abuse. The impact on reproduction and the health of children born from drug abusers is also of crucial concern.

Morbidity and especially the risk of contracting AIDS has brought a new dimension to the public health risk of intravenous illicit drug use [51–56]. Not only morbidity but also mortality may be a direct consequence of drugs and

other substances of abuse. In the United States, even though the use of illicit drugs by the general population significantly decreased in 1984 and 1988 according to the National Institute on Drug Abuse, there was a significant increase in emergency department visits and associated mortality for heroin, cocaine, marijuana or hashish and phencyclidine as reported by the Drug Abuse Warning Network [2]. This increased mortality has been documented by other studies [57–60].

Therapeutic measures, protocols and programs have been extremely varied which is no surprise when one considers the many controversies about the etiological (organic, psychological or social) factors of addiction and abuse [40,61-65]. Expectations of the public and also the courts of law used to be unrealistic and subjected to frustrations and deceptions when they are not met by addicts. The public perception of a disintoxication program is generally the same even though it may mean just a few days in a general hospital or a long-term in-patient cure in a specialized institution followed by many months of out-patient follow-up. In both instances, the individual is expected to return to a normal and productive life whatever his social, familial, financial or mental condition. Relapses are generally considered the patient's responsibility and not a failure of the treatment program. This attitude is generally observed irrespective of the quality and quantity of the therapeutic programs offered. This public perception is quite understandable when reviewing the scientific literature and the way it is reflected in the lay press. It is pretty confusing to observe the extreme diversity of therapies offered, all considered to be the most promising, if not the most effective. They extend from one extreme (strictly pharmacological) to another (strictly social or behavioural). For example, some authors consider that "aversion" therapies like antabuse for alcoholism or naltrexone for opiate addiction are highly effective. Others consider these approaches are repressive and useless if not actually dangerous. Abstinence is another matter of controversy which started many years ago in relation with the treatment of alcoholism. The Alcoholic Anonymous approach is a good example of the pro-abstinence philosophy. The same concept was later adapted to drug addiction. As a contrast to this, the British and the Dutch developed the concept of substitution therapy using either morphine or methadone for narcotic addicts. Methadone was also used alone or in combination with other therapeutic approaches in North America. The treatment of withdrawal syndromes is also an area of controversy. For example, many North American clinics for narcotic addiction will only offer a "cold chicken" treatment of withdrawal, which means that no medication is used, only the psychological and personal treatment by ex-addicts and therapists. On the other hand many other clinics, especially those located in medical institutions, will use various drugs in decreasing doses in order to prevent withdrawal symptoms. Methadone, morphine or codeine are used for opiates; chlordiazepoxide or diazepam for alcohol or benzodiazepines; phenobarbital for barbiturates. Clonidine is also used to alleviate the symptoms of withdrawal from opiates. Many other psychoactive drugs are used in addition to other therapeutic approaches. Various

psychotherapeutic techniques have also been promoted along with social re-insertion, peer and family support, ergotherapy, occupational therapy and even religious support.

Finally, the role of health professionals, other professionals and scientists in the arena of legal control or liberalisation of substances of abuse has been far from negligible [66–69]. It is, however, difficult for these professionals to maintain a strictly objective attitude when using their scientific or professional titles to increase the credibility of their personal opinion. Finding the ideal position between a passive and tolerant attitude and a militant or interventionist behaviour is a great challenge for everyone in the health, educational, social or scientific sectors.

SUBSTANCES OF PRESENT MAJOR CONCERN

Cocaine

Cocaine was used widely as a prescription or popular drug in the United States at the turn of the century. It was only after the Pure Food and Drug Act of 1906 that the Coca-Cola Company decocainized coca leaves [70]. The Harrison Narcotic Act made it illegal, as with heroin, in 1914. It only emerged as an illicit drug in the 1960s. Its use progressively increased in different classes of the society over the following 20 years with a peak in the early 80s. Since then, the pattern of abuse has changed progressively, decreasing in some sub-groups of the population like the middle-class, and also increasing in others like the low-income class, the ethnical minorities, the law-offenders but, at the same time, in the wealthy professionals, businessmen and sport professionals [71]. The phenomenon reached an epidemic level with increasing morbidity and mortality [72]. Clinical effects and medical management are well described in recent textbooks [70–73].

The importance of the problem in the United States stimulated both fundamental and clinical research on the various aspects of cocaine toxicity. This research was essential because of the significant changes that occurred in the pattern of cocaine abuse. This substance has a hundred-year history of abuse. However, it was not generally used in a compulsive manner, sometimes in episodic prolonged binges using high doses at it is now. This may explain why, until 1980, cocaine was considered incapable of producing physical dependence [74]. Another possible explanation that cocaine could assumedly produce psychological dependence only, may originate from the definition of the withdrawal syndrome that would follow the abrupt cessation of a drug for which progressive tolerance developed. This definition was established on the model of alcohol and opiate dependence. Withdrawal was then characterized by hyperreactivity: nervousness, irritability, insomnia, tremulations, convulsions, and hallucinations with alcohol; nervousness, insomnia, pilo-erection, mydriasis, abdominal and muscular cramps, and rhinorrhea, with opiates. However,

these substances are CNS depressants and it is not surprising that overstimulation is a characteristic of withdrawal. As cocaine and amphetamines are CNS stimulants, depression should logically be expected to occur during withdrawal, as it turned out to be. However, most authors refused to consider depression as a withdrawal syndrome and, hence, claimed these substances did not cause physical dependence.

More recent studies on the neuropharmacology of cocaine dependence have changed this view [75]. Animal models have shown that the reinforcing actions of cocaine intravenous self-administration seem to be mediated by pre-synaptic release of dopamine in the nucleus acumbens and involve predominantly dopamine D_1 receptor sub-type. The localisation of this "reward system" in the nucleus acumbens was also demonstrated in humans using positron emission tomographic scanner (PET) [65]. The withdrawal syndrome was also confirmed to occur in patients [76,77] and is characterized by transient craving, hyperactivity, slight tremor, insomnia and apprehension. Depression is also a significant symptom. Weddington [77] suggested to use the word "short-term abstinence" instead of "withdrawal" to describe this phenomenon in the course of which the pattern of REM sleep is greatly disturbed [78]. The finding that chronic stimulant abuse leads to neurophysiological adaptation has stimulated a lot of research on the potential use of pharmacological substances to alleviate cocaine-induced withdrawal syndrome [79]. The long-acting dopamine agonist bromocriptine was shown to reverse the post-cocaine anhedonia in the cocaine self-administration rat model [80]. Other drugs, namely desipramine, amantadine, bromocriptine, carbamazepine, fluoxetine, tropamine, and pergolide mesylate, have been evaluated in man [81–87]. Carbamazepine has also been evaluated as an adjunct to the treatment of crack use [88]. Methadone maintenance associated with desipramine and amantadine was also suggested as a possible therapeutic approach for cocaine dependence [89,90].

The effect of cocaine use on the pregnancy outcome and the fetus has been the matter of many recent reviews and studies [91–98]. The main effects of cocaine use during pregnancy involved low birth weight, low gestational age, small weight for gestational age, decreased head circumference, abruptio placentae and perinatal death. Intra-cerebral hemorrhages, neonatal behavioural effects ("the cocaine baby syndrome") and impaired psychomotor development have also been described. However, these studies are difficult to conduct because of the many confounding variables involved. A meta-analysis of the relationship between gestional cocaine use and pregnancy outcome [98] showed that very few clear conclusions can be drawn.

Phencyclidine

This drug was introduced in 1960 as an anesthetic agent. However, its use in humans was soon discontinued because of adverse psychological reactions. It is still used as a veterinary drug. It came to the illicit market in the United States in the mid 60s. It was reintroduced for a short while on the market in

the 70s and generated an important abuse as a street drug [70]. Interestingly, it has been sold under numerous street names like Angel Dust, Crystal, Mescaline, Peace, etc. It is still widely used in some areas of North America as a cheap drug for younger teenagers, delinquents and as a substitute for more expensive drugs like cocaine.

Ketamine, which is chemically related to phencyclidine, is still used as a dissociative anesthetic agent causing little respiratory depression. It is less potent and short-acting compared to phencyclidine. If phencyclidine is still popular nowadays as a "cheap" drug, this is because it can be relatively easily synthetized in illicit laboratories.

The finding that phencyclidine (PCP) was able to induce episodes of schizophreniform psychosis in some users promoted many fundamental and clinical research projects. PCP and ketamine were shown to produce most CNS effects through a reduction of the N-methyl-d-aspartate receptor sub-type (MMDA), which initiated even more research in two main areas: the therapeutic potential of PCP and related substances, and the etiological factors of schizophrenia [99,100].

Many substances were found to interact with the MMDA/PCP receptor/ion channel complex, called the PCP/sigma receptor for a certain time. The relation to sigma opiate receptors [101,102] was later denied and the nomenclature changed accordingly. The characterization of PCP pharmacological effects both on the central nervous system and peripheral tissues and organs is still in progress and the complexity of PCP action on various neurotransmitter systems and excitatory amino acids like glycine has recently been illustrated [103,104]. The behavioural effects of PCP resulting in both positive (i.e. hallucinations) and negative (i.e. emotional withdrawal) symptoms of psychosis are different from those of amphetamines [101,105,106].

Acute PCP overdose is a frequent cause of referral to the emergency room [107] with three different stages of the clinical presentation: Stage one, or mild intoxication is characterized by agitation and psychiatric symptoms; stage two by stupor and reactive coma; finally, in stage three, the patient is deeply comatose with tachycardia, hypertension, nystagmus and fever [108]. Rhabdomyolysis sometimes followed by acute renal failure is a possible complication [109]. Body packing and body stuffing occurs with PCP as with other drugs. Protracted coma may then follow. Decontamination of the G.I. tract is not an easy task because of the risk of rupture of the swallowed containers (i.e. condom or plastic bags) [111]. Fortunately, PCP chemical identification and assay are generally available [112].

PCP use by pregnant women does represent a significant risk for the fetus and the newborn [113,114]. PCP seems to have a profound impact on cultured cerebral cortical neurons and may inhibit neural circuitry in the human fetus [115]. PCP use is often associated with violent and criminal behaviour. It is however debated whether PCP is the etiological factor or the association is only indirect. It is well known that many criminals invoke PCP use as an excuse for their behaviour [116].

Cannabis

Even though cannabis has been used by man for thousands of years, people are still wondering what effects it may have on health. This is the best example of an area of research in which social, cultural, moral and legal aspects have a significant influence even on scientific and biomedical research. As an example, Nahas has been extremely productive in both the scientific literature [117] and the lay press. However, Goldfrank [73] considered him as a highly political source of drug information.

The acute toxicity of cannabis is low and there are no reports in the literature of a lethal overdose in man. The long-term regular use, however, cannot be without consequence. The inhaled smoke from marijuana or hashish contains the same chemical contaminants as cigarette smoke; these include acetaldehyde, acrolein, carbon monoxide, nitrosamine, and toluene along with higher concentrations of recognized carcinogens (benzanthracene, benzopyrene) [118].

Unfortunately, no large epidemiological studies similar to those related to cigarette smoking have been performed on cannabis use. This may explain reported discrepancies. There is no reason to believe, however, that heavy marijuana smoking would not produce the same deleterious effects on the lungs, the cardiovascular system and the fetus as those produced by tobacco smoke.

The acute effects of cannabis use on the brain (euphoria and dysphoria) have long been documented in the medical literature, but long-term psychological and neurological effects after prolonged use are still debated [119,120]. Most studies in this area have failed to control the various confounding variables, especially the concomitant use of alcohol and other drugs. The majority of studies were conducted in the 70s and 80s. Later on, cocaine instead of cannabis became a top priority for scientific and medical research. Self-reported drug use data is always a matter of controversies even though it is used in most studies. The kinetics of active ingredients, especially Δ-tetrahydrocannabinol (THC) and the low levels measured in blood do not allow a proper quantification of exposure. In fact, few studies have confirmed the self-reported drug use by laboratory measures [121–124].

A limited number of studies have been published on cannabis use, adverse effects and management in both developed and developing countries [17,125–130]. Contradictory results have been reported on the impact of cannabis use during pregnancy and lactation, especially because the first studies were conducted on mothers abusing alcohol, tobacco and other drugs [131,132]. Negative results on the impact of marijuana in pregnancy outcome, neonatal outcome and post-natal consequences in school-age children have also been published [133–135].

Solvents

Many volatile and gaseous substances have been abused since the first discovery of ether and chloroform. They still represent a matter of interest and

concern not only for health professionals but also for the general population because solvent abuse is associated with significant morbidity and mortality especially among children and specific populations such as aboriginals, North American Indians and other low-income minorities [136].

Many different substances are being used for their intoxicating effects: aliphatic and aromatic hydrocarbons, ketones, alcohols, esters, halogenated hydrocarbons, as extensively reviewed in Chapter 23 of this volume. Sniffing gasoline, adhesives, plastic cement and thinners, typing-correction fluids, fluorocarbon propellants follows a variable trend in popularity in various regions of the world [137]. The choice of the abused substance is generally related to a low cost and easy availability and not to a high efficacy or low toxicity. Solvents are mainly abused by children and teenagers who may be subdivided into three different categories [138]:

1. experimenters, namely those who try solvent abuse but do not stick to the habit;
2. regular abusers who maintain the habit for week or months;
3. long-term abusers.

The method of solvent inhalation is critical for clinical effects and medical complications. For example, holding a plastic bag full of solvent over the mouth and nose may induce a loss of consciousness. If the bag is left in that position, asphyxia may ensue. The combination of asphyxia with the arrhythmogenic properties of the solvent may induce severe cardiac arrhythmias and sometimes, death [139–141]. Long-term complications of solvent abuse vary according to the specific toxicity of the chemicals involved. Liver, kidney, and bone marrow injury, myopathy, polyneuropathy, rhabdomyolysis, metabolic acidosis and electrolyte imbalance may be seen [142]. In long-term abusers, organic brain syndrome may develop with permanent damage or slow recovery [143–147]. It is sometimes difficult to distinguish between psychological problems of the abusing children and teenagers and the toxic effects of the solvents [148]. Even though solvent abuse has been well described in the past [149–155], it is far from being under control and children are severely affected by a vast array of readily available volatile chemicals [156–159].

Opioids

Concern about the addictive potential of opium dates back to the 18th century. Following opium, the natural alkaloids, morphine, codeine, thebaine and papaverine came into use, followed by many semi-synthetic and synthetic substances. The main objective was to identify a drug which would retain the analgesic property of morphine without adverse effects (namely, tolerance, physical dependence, respiratory depression, constriction of the biliary tract, constipation). Partial agonists and antagonists were also developed and used clinically. Only the pure antagonist naloxone has not been subjected to abuse or non-medical use. Its very high affinity for opiate binding site of the μ receptor site type and low affinity for the k and Δ receptors accounts for this advantage

over earlier agonist-antagonist agents like nalorphine or levallorphan. Proper evaluation of abuse liability testing is now part of the pre-clinical and clinical evaluation of new drugs [160] especially by studying self-administration and drug-seeking behaviour.

Even though the pharmacological properties, medical indications and adverse effects of opioids have been well described, opioids are still widely under-used by physicians. The fear for adverse effects and especially of tolerance and physical dependence results in unnecessary pain in patients [161]. When used properly (adequate dosage of the proper medication required to suppress pain) in a medical setting, opioid addiction is a smaller problem than generally assumed.

Non-medical use especially of heroin hydromorphone, oxymorphone, meperidine, levorphanol, oxycodone, propoxyphene, pentazocine and more recently fentanyl is still a matter of public health concern. The transmission of AIDS in intravenous heroin addicts has increased morbidity and mortality in that population. Except for the risk of infections and acute overdose, opioids produced very little organ lesions even after prolonged use. This explains why drug substitution programs with morphine or methadone have been promoted. Methadone was clearly the drug of choice in North America because it can be administered by mouth thus reducing the liability of dependence [162] and has a long duration of action, allowing for a single daily administration. However, many opponents disclaim methadone use for the treatment of narcotic addicts. The reasons are extremely diverse but not always supported by objective data. On the contrary, many studies support the safety and efficacy of substitution treatment [163–169]. The experience gained has clearly shown that time is an important factor in achieving complete abstinence in these patients and that psychological, social and financial support is also required. The use of buprenorphine and a combination of buprenorphine–naloxone did not seem to control the intravenous misuse of buprenorphine in New Zealand [170]. The use of the central α_2 adrenergic receptor agonist clonidine to reduce withdrawal symptoms in narcotic addicts has gained popularity, especially in outpatient clinics.

The impact of opioid abuse during pregnancy and withdrawal syndrome in newborns of addicted mothers should be considered seriously by physicians in the prevention of severe complications, as has been well reviewed by Zagon [171].

Amphetamines, designer drugs and hallucinogens

The pattern of drug abuse has varied in different countries especially during the last three decades. In an extensive review of trends and consequences of drug abuse between 1980 and 1989, Senay [3] described the North American model (i.e. the U.S. and Canada) and compared it with the situation in Europe, Africa, Asia and Western Pacific. This review is a very useful source for those who wish to get a descriptive picture of the scientific studies conducted in the past thirty years. Unfortunately, the author did not criticize the methodology of these studies and tended to give each one an equivalent weight of evidence.

The toxicological properties, adverse effects and treatment of stimulants, designer drugs and hallucinogens have been addressed in recent toxicology textbooks. The abuse of amphetamines both as prescription or over-the-counter drugs as anorectics, and as street ("speed") drugs was prominent in the 60s and 70s in North America. Amphetamines were progressively replaced by cocaine as a stimulant and to phencyclidine as a psychodysleptic agent. However, it is still the drug of choice for abuse in some countries of Africa, Eastern Europe and Asia [15]. Epidemics of stimulant abuse have occurred cyclically following the introduction of new molecules on the market [172]. As seen during the 1994 World Football Cup, stimulants are still popular among professional players.

In Africa and Arabian countries, khat abuse has prevailed for centuries owing to euphorizing and psychotostimulant properties and is still abused by large portions of these populations [173,174]. It has even been air-freighted to the Somali community in Rome and other European capitals where it was considered as a social event [175]. Heavy consumption may lead to toxic psychosis [176].

In North America and Europe, the media has paid much attention to an exotic class of street drugs, the designer drugs [177]. Even though they are referred to as ecstasy (MDMA), love drug (MDA), serenity/tranquillity/peace (DOM/STP), speed, ice, meth (methamphetamine) as derivatives of amphetamines, or persian white, china white, fentanyl, 3-methylfentanyl, alpha-methylfentanyl as derivatives of the narcotic fentanyl, their impact on public health is still limited [178–181].

Pure hallucinogens like LSD are now very seldom encountered in most regions of the world. However, they are still used. It is important to be aware of their capacity to produce toxic psychosis [181]. The same is true for hallucinogenic mushrooms [182].

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Human Toxicology, J. Descotes (Ed.)

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19. Metals

Most metals are trace elements required for a normal functioning of the body, as they have been shown to be involved in over 200 essential metabolic pathways [1]. Another common feature is that metals can be toxic by inhibiting enzymic pathways, in lysosomes or mitochondria. Interestingly, varied chemical entities of the same metal may exert widely different toxic effects, suggesting that speciation is likely to be critical in the understanding of metal toxicity to humans as well as other species or systems.

As many studies have been devoted to the understanding of metal toxicity, it is beyond the scope of this chapter to cover all aspects of this topic. Particular emphasis will be given to those metals or to those toxic effects related to individual metals which have been the matter of recent concern or extensive investigations.

ALUMINIUM

Aluminium is a ubiquitous element in nature. It is the most common metal, comprising approximately 8% of the earth's crust as the mineral aggregate bauxite. Its toxicity is of increasing concern, especially because of potentially neurologic effects, and several studies have recently focused on the putative association of aluminium in the drinking water with cognitive impairment or Alzheimer's disease.

Aluminium toxicity in chronic renal failure

Aluminium toxicity is a well-known hazard in patients with chronic renal failure [2]. Altered renal function reduces the excretion of aluminium by the distal nephron and may induce overload resulting from contamination of dialysis water and from the use of aluminium-containing phosphate binders. Manifestations of toxicity include dementia, vitamin D-resistant osteomalacia, and microcytic hypochromic anemia. Aluminium may also affect the parathyroid gland.

This problem is of lesser importance since the advent of dialysate fluids purification and new antiulcer drugs resulting in the minimised use of alu-

minium-containing drugs. Encephalopathy and osteomalacia can be treated by repeated injections of desferoxamin during hemodialysis. In the future, the development of effective and safe phosphate binders without aluminium would be interesting.

Adverse effects at the workplace

Exposure to aluminium may also be an occupational hazard. Aluminium and its derivatives essentially cause acute irritant dermatitis or respiratory irritation. Repeated inhalation of aluminium powder and dust may induce asthma-like syndrome probably due to irritation rather than allergy, chronic obstructive lung disease, and exceptionally pulmonary fibrosis. A recent case-match study of 670 aluminium workers in Alabama found a higher prevalence of asthma, wheezing, airways obstruction, and irregular opacities on chest X-rays than in controls, with an aggravating role of smoking [3]. Long-term inhalation exposure to aluminium may give rise to accumulation in the body of exposed workers, even in the absence of renal failure [4]. Uncoordination and some cognitive defects such as memory loss, impairment in abstract reasoning, and depression, have been observed in aluminium smelters and also in miners exposed to aluminium powder used until 1979 as a prophylactic treatment for silicosis [5–7].

Rönneberg and Langmark [8] reviewed 11 separate epidemiologic studies of cancer in aluminium workers. The association between aluminium and bladder cancer is the best documented and an increased risk between 1.5 and 4.5 was shown in aluminium-smelting workers from plants using the Soderberg process. These studies suggested a latency of more than 20 years from the start of exposure to the time of cancer diagnosis. A statistically significant excess of lung cancer in aluminium workers was inconsistently found and when present, it was not compared with smoking data. The risk associated with other cancers is far less well documented.

Aluminium and Alzheimer's disease

The undoubted role of aluminium overload in dialysis encephalopathy and the findings of increased aluminium levels in both dialysis encephalopathy and Alzheimer's disease led to the assumption that aluminium could also be involved in Alzheimer's disease [9,10]. Analytical studies indicated the presence of aluminium in the primary histopathological lesions of patients with Alzheimer's disease.

Subsequently, early epidemiological data reported a correlation between aluminium levels in water supplies and increased rates of probable Alzheimer's disease-type dementia. But the earlier histopathological findings were not always reproduced, especially when more sensitive assays were used, and the suggestion was made of a contamination with aluminosilicates during the processing of neuropathological samples. In addition, a recent epidemiological study conducted in the western part of France did not confirm previous findings

[11]. This study found no independent effects of aluminium in samples of drinking water on the prevalence of cognitive impairments. After adjustment of age, gender, levels of education and occupational activity, a weakly increased risk of high aluminium levels, if associated with a low pH, was shown. On the other hand, a high pH was found to reduce the risk. Thus, the relative risk of aluminium in drinking water is seemingly very low, if at all present. All epidemiological results were based on ecological analysis only, studying geographical distribution of diseases between regions with different levels of aluminium in drinking water, and were not based on individual analysis with a direct estimation of exposure [9]. Actually, aluminium is also found as various forms with varying capacity of duodenal absorption. Aluminium comes from a variety of dietary sources among which drinking water represents only about 10%.

Other sources of aluminium should be included in the direct estimates of individual exposure. A large case-control study, the Canadian Study of Health and Aging, was held in elderly individuals in Canada [12]. This study provided little evidence supporting the hypothesis of an association between aluminium and Alzheimer's disease. Results did not show an association between the use of aluminium-containing antiacids and Alzheimer's disease. The odds rates for tea consumption, a beverage with a relatively high amount of aluminium, was not significantly elevated, as well as for aluminium-containing antiperspirants, although the information recorded about the latter was incomplete [10].

Aluminium as a sensitizer

Aluminium is a weak sensitizer. Nevertheless, aluminium-induced contact sensitivity has been observed following the use of antiperspirant sticks [13]. Dwyer and Kerr [14] described contact dermatitis in two young brothers with positive patch test for aluminium and discussed the possibility that aluminium allergy may be less uncommon in children than in adults. Recent publications described the potential role of aluminium in delayed hypersensitivity occurring with diphtheria tetanus pertussis or hepatitis B vaccines, and also with aluminium-precipitated antigen solutions used for hyposensitization therapy, with persistent cutaneous granulomas [15–17]. Nevertheless, a recent double-blind clinical trial in 235 children aged 10 years found fewer extensive local reactions with aluminium-adsorbed diphtheria–tetanus vaccine than with the same vaccine in a fluid formulation. The distribution of systemic and globally local reactions were equal in both groups [18].

MANGANESE

Environmental and occupational exposure to manganese has been associated with neurological disorders mimicking Parkinson's disease. Occupational exposure to manganese dust may also affect the lungs, with an increased incidence of pneumonia, bronchitis and chronic non-specific lung disease. The extraction of manganese in mines, the production and treatment of steel, arc

welding and the manufacture of dry cells, are the main circumstances of manganese occupational exposure.

The onset and development of manganese-induced parkinsonism are insidious. The early clinical stage includes non-specific symptoms like asthenia, anorexia and apathy, and sometimes psychiatric prodroma (e.g. hallucinations, psychosis). The following stages are usually irreversible and progression is possible even long after the cessation of exposure [19].

Recent studies have focused on the identification of exposure biomarkers and the detection of early abnormalities to prevent irreversible damage. A cross sectional study was performed in workers from a large ferromanganese and silicomanganese alloy facility to document early nervous system dysfunction associated with long-term manganese exposure [20]. In the exposed group, significantly higher blood levels of manganese were associated with altered neurofunctional tests (symptom reporting, emotional state, motor functions, cognitive flexibility, olfactory perception threshold). Similar neurological symptoms, with poorer performance on visual reaction time, eye-hand coordination and hand steadiness, were observed in workers from a battery plant [21]. These symptoms were related to the lifetime integrated exposure to total and breathable manganese dust. Nelson et al. [22] recently discussed the potential value of early magnetic resonance imaging, as the paramagnetic properties of manganese may induce transient suggestive changes.

How manganese can induce parkinsonism is not well understood. Parkinson's disease is linked to a degenerative loss of neurons in the substantia nigra pars compacta of the basal ganglia, and subsequently to a loss of dopamine secreted by these neurons. Symptoms occur when dopamine secretion is reduced by more than 80%. Manganese, like other metals (e.g. iron and copper) can favour the production of free radicals by auto-oxidation of dopamine [23], resulting in the peroxidation of adjacent tissues, such as lipids. Manganese may act directly or indirectly, by displacing iron from its complexes with neuromelanin, and thus increasing free iron in the neurons.

$CaNa_2$ EDTA chelator may be successfully used to treat mild manganese poisoning, but the treatment of end-stage Parkinson's manganism is usually only symptomatic. Responses to levodopa were shown to differ from those of patients with Parkinson's disease [19]. Shuqin et al. [24] recently reported two cases of chronic serious manganese poisoning treated with para-aminosalicylic acid. After treatment, symptoms gradually improved and disappeared, and a 19-month and 6-month follow-up for patients 1 and 2 respectively, found no signs of recurrence. Thus, PAS-Na may be an interesting development in the specific treatment of manganism. Nevertheless, the mechanism of its action remains unclear and further research is warranted.

SILVER

The most typical consequence of silver exposure is argyria, a condition characterized by a discolored skin on the hands, and later the face. Deposits on

the cornea (argyrosis) develop early and may result in impaired visual acuity. Nephrotoxicity was a common complication of treatment with silver-containing medicines.

Argyria related to occupational activities, especially the production of silver nitrate, has almost disappeared, but several cases of iatrogenic localized or generalized argyria were recently published [25–28]. The question of a potential neurotoxicity is still unsolved even though silver is usually thought to cause no pathological complication, except for an irreversible esthetical damage.

CADMIUM

Cadmium is a cumulative occupational and environmental pollutant that may persist for an exceptionally long period of time in the human body (half-life in the range 10–30 years). It accumulates mainly in the kidneys and the liver. The kidney is usually considered as the critical target organ of cadmium toxicity, but the lung and the bone may also be affected. Its great interest in toxicology comes from the assessment of validated markers of early nephrotoxicity, based on various urinary (low- and high-molecular-weight proteins, enzymes, tubular antigens) or blood (β_2-microglobulin, creatinine) parameters.

Sources of cadmium exposure

Chronic exposure is an occupational hazard, particularly during smelting and welding. Cadmium is used in alloys with steel, zinc, copper and lead, and in the manufacture of nickel/cadmium batteries. Cadmium salts are used as pigments in paints, especially cadmium sulfide as a yellow pigment, and as stabilizing agents in the industry of plastics. The inhalation of dusts and fumes containing cadmium is the major route of exposure in the occupational setting [29].

Several years ago, cadmium became known as an important environmental pollutant which may give rise to accumulation in the body and induce health effects, particularly renal damage, in the inhabitants of polluted areas. Indeed, the release of cadmium into the environment has considerably increased during the last fifty years in most industrialized countries. The general population is mainly exposed by the oral route, via cadmium-contaminated well-water and crops grown on polluted soils [30]. Tobacco smoke was also recognized as an important source of cadmium, and the body burden of smokers is about twice that of nonsmokers [31]. The fact that environmental pollution may influence the cadmium body burden of the general population is now well recognized. This has been confirmed by a large cross sectional study, the Cadmibel Study, which was conducted over four years in different areas of Belgium, an important producer of cadmium in Europe (one fourth of the whole European production) [32]. After standardization to age and adjustment for significant covariates, results showed that urinary cadmium levels differed significantly according to the place of residence. Even though the relation between urinary cadmium

levels and the degree of cadmium soil pollution was not exactly linear, the highest cadmium urinary levels were found in the two most polluted areas and the lowest in the less polluted area [32]. Cadmium levels in the renal cortex of Europeans have been estimated to have increased 50-fold due to environmental cadmium pollution since the beginning of this century [33].

Early biomarkers of cadmium nephrotoxicity

The definition of dose-related biomarkers as well as the potential carcinogenic effect of cadmium has raised great concern during the recent years. Recent works have attempted to define early markers and to refine biological exposure limits, for industrial workers as well as for residents of polluted areas. The kidney is the major target organ of cadmium toxicity. Renal effects of cadmium are observed in industrial workers as well as in the inhabitants of cadmium-polluted areas. Increased proteinuria, usually less than 2 g/24 hours, is the earliest sign of cadmium-induced proximal tubular nephropathy. At this stage, proteins excreted in the urine are essentially low-molecular-weight proteins, including β_2 microglobulin, retinol-binding-protein and N-acetyl-β-D-glucosaminidase. Glomerular dysfunction with albuminuria, increased excretion of glucose, amino acids, calcium, phosphorus and uric acid may follow. The follow-up of workers with cadmium-induced renal damage evidenced by increased urinary excretion of β_2-microglobulin or retinol-binding-protein, confirmed the irreversibility of these changes [34,35]. Numerous studies have been carried out to refine biological indicators of exposure, body burden and the early nephrotoxic effects of cadmium. In moderately exposed workers, blood levels are mainly indicative of recent exposure (last 3 to 4 months), especially in newly exposed workers. Urinary excretion is usually the best indicator of cadmium body burden at low exposure levels, in workers as well as the general population. In cadmium-exposed workers, a urinary concentration of about 5–10 μg/g creatinine was shown to be associated with a 10% probability of renal damage with enzymuria or proteinuria. These values were found to correspond to an average cadmium concentration in the kidney cortex of 100–200 ppm (mg/kg) wet weight [36].

To assess markers of early renal changes induced by occupational exposure to cadmium, a study was recently conducted in 37 male zinc and cadmium smelters (mean duration of exposure 11 years) and 43 controls. Urinary and blood cadmium levels were on the average 6 to 8 times higher than in controls. A dose-effect response could be shown between these levels and most of the studied markers. The duration of exposure was significantly correlated with several urinary markers, namely albumin, transferrin, IgG, β_2-microglobulin, retinol-binding-protein, N-acetyl-β-D-glucosaminidase and the tubular antigen, intestinal alkaline phosphatase. A relation with the duration of exposure was also found with β_2-microglobulin in serum. Urinary 6-keto-PGF1α followed by urinary sialic acid and tubular antigens or enzymes, appeared to be the most sensitive markers. The prevalence of abnormal values of the 3 latter markers

in the cadmium-exposed group were 49%, 35% and 20%, respectively. The determination of urinary prostaglandin in cadmium-exposed people looks interesting for further research, as it could help in the understanding of the mechanism of cadmium-induced nephrotoxicity [37].

Results from the Cadmibel Study suggested that tubular dysfunction might be induced by environmental cadmium because a significant and positive association between several markers of nephrotoxicity (urinary excretion of retinol-binding-protein, N-acetyl-β-D-glucosaminidase, β_2-microglobulin, amino acids and calcium), and the urinary excretion of cadmium was found. The internal dose of cadmium in about 10% of the general population of Belgium was estimated to be sufficient to cause slight renal dysfunction. These conclusions can presumably be extrapolated to most of the industrialized countries using large amounts of cadmium [33]. The risk of renal damage in inhabitants of cadmium-polluted areas was assumed to be higher than in cadmium-exposed workers, indicating that the threshold level should be lower in the general population than in occupational settings [38]. Indeed, the occupational threshold level calculated for healthy workers, may underestimate the risk for particular target groups of the general population, like elderly subjects or people with previously altered renal function. Diabetics also appeared to be more susceptible to the proximal tubular nephrotoxicity of cadmium, as well as smokers, who have an additional source of cadmium exposure [33].

The threshold concentration of urinary cadmium for occupational surveillance has been a matter of controversy, between 10 μg/g creatinine as initially suggested, and 5 μg/g creatinine as proposed in view of the recent studies. The American Conference of Governmental Industrial Hygienists (ACGIH) recommended the level of 5 μg/g creatinine as the biological exposure limit for occupational exposure to cadmium. This value indeed tends to be supported by recent studies. For the general population exposed to environmental cadmium, the level of 2 μg/g creatinine has been proposed, which is usually the normal limit value of urinary cadmium [37].

Nevertheless, it is important to note that above 5 μg/g creatinine, the observed renal changes are essentially slight, with increased urinary excretion of tubular enzymes or antigens. The clinical relevance and the consequence of these changes on mortality are not well established. Markers predicting an overt nephropathy (e.g. low-molecular-weight proteinuria) are mainly observed with a threshold level of 10 μg/g creatinine [39]. The association between urinary β_2-microglobulin and mortality in inhabitants of polluted areas is supported by two recent Japanese studies which found a statistically significant association between urinary β_2-microglobulin and mortality from all causes [39,40]. However, the link between biological changes, like increased urinary excretion of tubular enzymes or antigens, and the subsequent development of an overt cadmium nephropathy remains to be elucidated and requires further research.

Another possible renal effect of occupational cadmium exposure is urolithiasis as observed in a study of cadmium-exposed battery workers [41]. The risk

was shown to be related to cumulative cadmium exposure and to be often associated with tubular proteinuria.

Hypertension

Cadmium has been implicated in the development of hypertension, but its role remains unclear. Cadmium was shown to induce hypertension in animals and studies in exposed people did not produce a definite conclusion. Effects on the cardiovascular system were suggested for the population living in cadmium-polluted areas, but this hypothesis was not confirmed by the Cadmibel study as no significant correlation between urinary cadmium levels and the prevalence of hypertension or other cardiovascular diseases was found [42].

Adverse effects on bone

The accumulation of cadmium may lead to osteomalacia and osteoporosis by interfering with the metabolism of vitamin D and calcium. These effects are usually observed following severe cadmium poisoning in exposed workers, but environmental exposure to cadmium is also suspected to contribute to bone diseases, particularly in subjects with contributing factors (age, hormonal or nutritional deficiencies). Urinary cadmium levels were found to be positively correlated with serum alkaline phosphatase activity and urinary calcium excretion, and negatively correlated with serum total calcium in residents of polluted areas [42].

Cadmium carcinogenicity

The carcinogenicity of cadmium compounds, especially cadmium oxide, chloride, sulphate and sulfide, has been extensively investigated in animals. Malignant lung tumours, and less frequently prostatic neoplasms or leukemia, have been observed after repetitive ingestion or inhalation in experimental animals. Injection-site sarcomas, interstitial Leydig cell tumors of the testis or prostatic tumors following cadmium injection, have also been described. Epidemiological data have suggested the possibility for an increased risk of lung and prostatic cancers in workers heavily exposed to cadmium [43]. Nevertheless, concomitant occupational exposures to arsenic or nickel, and smoking may be confounding factors, the importance of which have not yet been carefully evaluated. Available data about environmentally exposed human populations are limited and do not allow assessment of the carcinogenicity of cadmium following environmental exposure [44].

Cadmium and the lung

Fumes or particles of cadmium compounds may also have irritative acute effects on the bronchopulmonary or the gastroenteric tract. In the occupational

setting, the lung may also be affected by the inhalation of dusts or fumes containing cadmium. Acute occupational exposure to high concentrations of cadmium oxide fumes may induce a chemical pneumonitis in smelters or welders, which is characterized by cough, dyspnea and myalgia, and secondary pulmonary oedema that may be lethal. Clinical symptoms of severe pulmonary irritation may occur after a latency from exposure, or may be announced by only minor warning symptoms [45]. Death occurs 1 to 3 days after exposure [29]. In addition, chronic occupational exposure may lead to respiratory illnesses (rhinitis, bronchitis, emphysema, chronic obstructive insufficiency).

Acute poisoning

Acute deliberate cadmium poisoning is rare, but fatal poisonings with large tissue destruction and multivisceral failure have been described after massive deliberate ingestion of cadmium iodide or cadmium chloride, 5 g and 150 g respectively [29,46].

MERCURY

Metallic mercury is used in alloys with several metals (e.g. silver, tin, copper, zinc), for dental amalgams, and in the manufacture of thermometers, barometers and fluorescent tubes. Mercury salts are widely used in the industry as catalytics, tanning agents, disinfectants, pesticides, and wood preservatives, and as pigments in paints.

The toxicity of mercury has been well known for a long time with the central nervous system and the kidney as the main target organs [47]. Acute exposure to high mercury levels induces respiratory irritation (dyspnea, cough, bronchitis, pneumonitis, chest pain), digestive disturbances, and severe renal damage. By contrast, chronic inhalation of mercury is associated with signs and symptoms of more insidious onset, including ear, throat and nose disorders like gingivitis and stomatitis, central nervous system dysfunction with intention tremor and psychological disturbances, peripheral neuropathy, and finally renal damage.

The majority of poisonings at the workplace are due to exposure to elemental mercury vapor resulting from the accidental breakage of mercury-filled thermometers and barometers, which readily vaporize at room temperature. In particular, dentists appear to be occupationally exposed to mercury, especially during the removal of old dental amalgams; a study of about 300 dentists in their fifth decade of life, showed excess mercury levels in 13% of them [13]. Workers in the chloralkali industry may be particularly exposed to vapors of elemental mercury used as a cathode in the electrolysis of brine, for the production of chlorine and caustic soda.

Neurotoxicity

Neurological impairment is the most prominent change in mercury intoxication. It is due to the high lipid solubility of elemental mercury that can easily cross the blood-brain barrier by diffusion, and accumulate within the cerebral cortex and the cerebellum. The syndrome, called erethismus mercurialis, includes finger tremor and disturbances of fine movements, postural tremor, insomnia, loss of appetite, emotional liability, and memory loss. Peripheral sensory nerves may also be altered. Recent studies have focused on long-term neurological abnormalities after the cessation of exposure to mercury vapours [48,49]. They showed impairment of both the peripheral and central nervous systems, indicating that neurological abnormalities may persist many years after exposure had ceased, even more than ten years. These abnormalities are however usually mild, including clinical changes like increased prevalence of deterioration of short-term memory, postural or finger tremor, disturbed coordination, alterations in visual evoked responses, and peripheral motor or sensory nerve defects on neurographic examination.

Ellingsen et al. [50] further studied the relation between different indices of mercury exposure (based on estimates of cumulative mercury levels in air and urine), and neurological results. The study was conducted in 77 retired chloralkali workers examined on average 12.3 years after the cessation of exposure to mercury and who had been exposed for an average of 7.9 years, as compared to 53 age-matched controls. Results found a significant association between the calculated cumulative mercury level in the atmosphere and median sensory nerve conduction velocity. An association between cumulative urinary mercury levels and the amplitude of the sural nerve was also suggested. A dose–response relationship was difficult to assess because the observed neurological abnormalities were mild and most of the exposed subjects had low levels of exposure.

Other studies in workers with low exposure found more alterations of performance in psychometric tests in relation to a longer duration or higher degree of exposure. These results are difficult to compare because different methodologies were used, in particular as regards the choice of exposure criteria, but nevertheless the effects of mercury on the central nervous system appeared to be slight [49,51]. It remains difficult to define a no-effect threshold as regards the central nervous system. The World Health Organization study group recommended an exposure limit to mercury vapour of 25 $\mu g/m^3$ in the air (TWA, Time Weighted Average) and a biological threshold concentration of mercury in the urine of 50 $\mu g/g$ creatinine [52].

Nephrotoxicity

Renal disturbances induced by repeated inhalation of mercury vapours are usually moderate with mild high-molecular-weight proteinuria, but nephrotic syndrome, glomerulonephritis which is usually of the immune-complex type,

and tubular cytotoxicity with enhanced urinary excretion of the enzymes N-acetyl-β-D-glucosaminidase and β-galactosidase, or retinol-binding protein, may also occur. Recent studies attempted to find markers of early renal changes in relation to indices of exposure, to prevent irreversible or severe renal damage. Several studies, however, have failed to find such markers. Two reasons might explain these findings [53,54]: firstly, the level of mercury exposure was low, generally below 50 μg/g creatinine, what is the usual estimation of the threshold limit value for the risk of nephrotoxicity associated with mercury vapours. Secondly, changes induced in such conditions are mild and their clinical relevance unclear.

A recent study [55] in 50 chloroalkali workers exposed to elemental mercury with an average duration of exposure of 11 years, and 50 controls, attempted to improve the assessment of the value of three categories of renal changes as possible markers of early nephrotoxicity induced by mercury: namely, functional markers (serum creatinine and β_2-microglobulin, urinary low- or high-molecular-weight proteins), cytotoxicity markers (tubular antigens and enzymes in urine) and biochemical markers (eicosanoids, fibronectin, kallikrein activity, sialic acid, and glycosaminoglycans in urine, red blood cell membrane negative charges). β_2-microglobulin appeared to be unrelated to blood or urine mercury levels. Increased urinary levels of tubular antigens and enzymes, and several biochemical alterations (decreased urinary excretion of eicosanoids and glycosaminoglycans, and lower urinary pH) were found to be more frequent in exposed individuals than in controls. In particular, some of these changes were found to be more frequent when urinary mercury levels were above 50 μg/g creatinine. Nevertheless, none of these effects were related to the duration of exposure, which can be perhaps explained by the low exposure level (mean urinary excretion of mercury = 22 μg/g creatinine).

A recent study [56] showed that a microprotein, the Clara cell protein (CC16) synthesized by the nonciliated tracheobronchial epithelium, and which diffuses passively by transudation into the serum, could be a very sensitive indicator of very subtle dysfunctions in the proximal tubule of subjects exposed to various pulmonary toxins. This protein appeared more sensitive than other classical markers, like β_2-microglobulin or retinol-binding-protein. Further investigations are in any case needed to assess the value of this protein as a marker of tubular nephrotoxicity in mercury-exposed people.

Skin toxicity

Some mercuric salts, particularly mercuric chloride, iodide or nitrate, are corrosive at high concentrations. Mercuric compounds and rarely metallic mercury, may cause contact sensitization. Most of the latent sensitizations observed as a positive mercury patch test, could be explained by the wide use of mercury-containing medications, like merbromin (Mercurochrome) and thimerosal, in the past. An underestimated source of mercury sensitization is related to the red color tattooing which contains mercuric sulfide and may

induce very pruritic contact dermatitis. A case of systemic intoxication was described after topical application of a metallic ointment [13].

Environmental contamination

The general population may be also threatened by mercury environmental contamination and two historical collective poisonings are particularly illustrative of adverse effects related to the ingestion of food contaminated by the organic compound methylmercury. The first epidemic was observed in the 1950s, among inhabitants around the Minamata Bay in Japan. Inorganic mercury rejected to the sea by a nearby chemical plant, was transformed into methylmercury by plankton, then plankton was swallowed by fish, and finally methylmercury-contaminated fish was eaten by fishermen and their families, of whom a number developed irreversible neurological damage and fetal abnormalities. The second epidemic was observed in Iraq in the winter of 1971–1972 with more than 6000 people intoxicated following the consumption of seed grains treated with methylmercury used as a fungicide, of whom 500 died.

Mercury exposure was also recently discovered in the Amazon basin where metallic mercury is used to extract gold from ore. Gold is purified by heating the amalgam formed with mercury and during this process, vapours are emitted. Environmental contamination is also of great concern because, during the process, mercury is lost and is ultimately released into the river. Up to 1200 tons of mercury have been estimated to have been rejected into the Amazon river basin.

In this region, several cases of mercury intoxication related to the use of this process have been observed in gold miners and also in riverside villagers. Branches et al. [57] reported 55 cases of patients with signs and symptoms consistent with mercury exposure, among them 40% who had no direct occupational exposure related to gold mining or refining. The most frequently reported symptoms were dizziness, headache, palpitations, tremor, numbness, insomnia, dyspnea, and nervousness. Mercury levels in whole blood and urine were 0.4–13 μg/dl (mean = 3.05 μg/dl) and 0–151 μg/dl (mean = 32.7 μg/dl), respectively. Occupationally exposed patients have been working as gold shop workers (where gold is refined and sold) or as gold miners for 2 to 44 years. Of potentially serious concern is the fact that social, professional and financial considerations make unlikely the possibility of a rapid solution, such as the removal of exposure, the improvement of individual protection, or the implementation of engineering control.

There was recently considerable controversy as to whether mercury amalgam fillings in the mouth can release mercury and if so, induce toxicity. Many epidemiological studies have attempted to reach a better definition of this potential link. Up to now, they have failed to find any close or constant positive association with mercury dental amalgams.

Cytogenetic studies in mercury-exposed workers have inconsistently observed chromosomal aberrations. There have been only a few reports from animal studies on the possible effects of inorganic or metallic mercury. Reports

on carcinogenic effects from epidemiological studies among exposed workers inconsistently showed a weak excess of different types of cancer, especially lung cancer [58]. But these results may be explained by smoking or a concomitant exposure to asbestos.

COBALT

Cobalt is a hard metal extensively used as a mixture with other metals to form high-strength alloys, especially tungsten carbide, or also nickel and aluminium in the manufacture of diamonds. Cobalt salts are also widely used as pigments in glass, ceramics, paints and varnishes, and as catalysts. Workers may be exposed to pure cobalt metal, cobalt oxides or salts, often in association with other substances such as metallic carbides. Exposure to cobalt is mainly by inhalation. Cobalt can affect several organs, like the lung, the skin, the thyroid, the heart and the bone marrow.

Lung toxicity

The main target organ of cobalt following occupational exposure is the lung [29]. Inhalation of cobalt may induce transient manifestations, like dyspnea, pharyngal irritation, sneezing, cough, that are mainly due to an irritative effect. Bronchial asthma, with wheezing, chest tightness, dyspnea and cough, is felt to be a type-I allergic response, because specific IgE antibodies directed against cobalt linked to albumin, have sometimes been detected [59]. Bronchial asthma induced by cobalt has a low incidence, estimated to be approximately 5% [60], and it usually improves after removal from exposure.

An interstitial lung disease is also a possible, but relatively uncommon consequence of exposure to cobalt in the industry of hard metals. Clinical features range from hypersensitivity pneumonitis or alveolitis, to diffuse pulmonary fibrosis. Alveolitis usually improves spontaneously upon the subject's removal from further exposure. Irreversible pulmonary fibrosis may develop gradually due to continuous exposure, with progressive aggravation and persistence of cough and dyspnea, and the onset of weight loss, asthenia and cyanosis. Lung function tests revealed restrictive ventilatory impairment and a reduction of the diffusing capacity. The radiological features vary greatly from linear and/or round opacities, to, exceptionally, no roentgenographic abnormalities [61]. The role of cobalt in this interstitial lung disease is well recognized, but as this disease was mainly described in the hard metal and diamond polishing industries, the role of other associated airborne pollutants such as tungsten carbide, titanium carbide or diamond particles, which could enhance the effect of cobalt, has also been proposed. The latter assumption tends to be supported by the results of a recent cross sectional study in 82 workers exposed to pure cobalt dust in a cobalt refinery [60]: dyspnea and wheezing were more frequently reported in the exposed than in the sex- and age-matched control group, whereas no differences in lung volumes, ventilatory

performance and carbon monoxide diffusing capacity were seen between both groups. Interestingly, this study found a significantly higher incidence of eczema and erythema in exposed workers compared to controls.

Other adverse effects

Several cases of allergic dermatitis have indeed been described in relation to metallic cobalt dust exposure or the use of cobalt salts. The abrasive character of soluble cobalt salts is thought to contribute to sensitization. Cobalt sensitivity may be occasionally involved in cement dermatitis. Photosensitivity caused by cobalt has also been reported [13].

The threshold limit value (TLV) for cobalt was set to 50 $\mu g/m^3$. A survey of 195 diamond polishers found that, for highly exposed workers, the lung function indices were lower than predicted, without relation to smoking habits, even though the air concentrations were always found to be below the TLV for cobalt, suggesting that cobalt exposure should be maintained well below the currently recommended TLV [62].

The role of cobalt in lung cancer is debatable and a conclusive association has not been yet established. An increased incidence of mortality due to lung cancer was described, but cumulative exposure to nickel and arsenic, or smoking, may be confounding factors [62].

The analysis of cobalt in urine or blood has been proposed as an indicator of recent exposure in occupationally exposed workers [63,64]. A recent study has been undertaken to assess the value of different chemical forms of cobalt as indicators of recent exposure [65]. The results showed that cobalt concentrations in the urine or blood reflect recent exposure to soluble cobalt derivatives. By contrast, cobalt oxides were suggested to poorly reflect recent exposure levels. A 8-hour exposure to 20 or 50 $\mu g/m^3$ of a soluble form of cobalt was shown to lead to an average cobalt concentration in post-shift urines collected at the end of the working week, of 18.2 or 32.4 $\mu g/g$ creatinine, respectively.

Myocardial degeneration attributed to cobalt used as an additive in beer was observed in Belgium and Canada in the 1960s. Clinical features included right and left, rapidly progressive, cardiac decompensation, with pericarditis, hypotension and cardiogenic shock.

The role of cobalt alone in the occurrence of other adverse health effects is debatable, because of the frequent association with exposure to other substances such as tungsten and titanium carbide, iron, silica and diamond. A recent epidemiologic survey in workers exposed to cobalt alone showed an increase of respiratory symptoms (dyspnea, wheezing) and skin lesions (erythema, eczema) [60].

CHROMIUM

Chromium occurs in several valence states with different physico-chemical and toxicological properties. Trivalent and hexavalent chromium are the most

abundant forms. While trivalent chromium is found naturally in the environment, hexavalent chromium results essentially from varying industrial activities and may constitute an occupational and environmental hazard. Trivalent chromium is an essential nutrient. It has a limited oral and dermal bioavailability and a low acute and chronic toxicity. On the other hand, hexavalent chromium is more extensively absorbed by all routes in humans and is classified as a known respiratory carcinogen. With respect to its known toxicity and because soils were filled with large amounts of chromite ore processing in various locations, especially in the United States until the 1970s, there has been growing concern about the assessment of human health risks related to chromium-contaminated soils [66].

The toxicity of chromium is essentially associated with hexavalent compounds and is due to their strong oxidizing potential. After penetration into the cell, hexavalent chromium is reduced to pentavalent and trivalent states, with production of free oxygen radicals which cause lipid peroxidation, cell membrane alterations, enzyme inhibition and DNA damage. This process leads to the production of free radicals thought to be involved in the cytotoxic and genotoxic damages caused by chromium. Hexavalent chromium appears to be 10–100 times more toxic than trivalent chromium [67].

Exposure to hexavalent chromium may cause tissue damage, irritative lesions of the skin and the respiratory tract. These symptoms, particularly nasal septum perforation, appear to be related to the degree of chromium exposure [68]. Contact dermatitis induced by chromium is well known. It is related to both irritation and, less frequently, cell-mediated allergy. Inhalation of chromium may induce lung cancer, but a significant excess of nasal cancer has also been observed in chromate production workers [69]. Nephrotoxicity of hexavalent chromium was shown in humans with acute and massive exposure, but Petersen et al. [70] recently reported the first case of chronic interstitial nephropathy in a patient who was occupationally exposed to smoke containing chromium, and had blood and urinary chromium levels, respectively seven and six times higher than the normal values.

Because of its known toxicity and wide industrial use, there has been great concern about the environmental pollution and subsequent risks for the general population. Two recent reports have focused on estimating the amount of chromium absorbed by the general population from the environment, and the possible health consequences [66,71] and concluded that the amount absorbed in the studied regions was far below that of occupational sites.

LEAD

Lead exposure results from many different sources of varying magnitude. Excessive exposure to lead particularly involves children who ingest dust particles and paint chips containing lead. Recently, this problem may also have been recognized to affect children of middle- and upper-class families during the renovation of old houses. In the United States, approximately 75% of the

pre-1980 houses were estimated to contain hazardous quantities of leaded paint with an estimated amount of 3 million tons of leaded paint in houses [72]. The highest risk was shown to be in children living in pre-1959 houses, which were shown to contain the highest lead concentrations in paint. The general population is exposed through air pollution by lead from vehicles using leaded gasoline or from lead smelters, and also through the drinking water. Food or various beverages may be contaminated by lead crystal decanters or ceramic pottery. Workers may be exposed to lead fumes and dust at the working place. An unexpected source of lead is related to the use of traditional ethnic remedies, particularly those of Asian or Mexican origin [73,74].

Human lead body burden

Average blood lead levels have decreased by approximately 5 to 10% in most of the industrial countries [75]. The first major cause of this appears to be the reduction of lead in gasoline after the introduction of catalytic converters, but the reduction of lead in widely dispersed sources, such as food and drinking water, has also contributed to this favorable evolution. In the United States, in the period 1976–1980, the number of children with lead levels above 15 μg/dl (0.72 μmol/l) was estimated to be 8.5 million and it fell to 3–4 million with a projection of the data to 1984, based on decreased exposure to lead from environmental sources, and primarily gasoline in the 1976–1984 period. The environmental exposure of children can be reduced by lead reduction or elimination in widely dispersed sources such as gasoline, food and water and also, of course, by developing programmes for abating lead from the home environment. This last approach is very difficult to implement and will take a long time to be completed, but it was shown that other methods can decrease the lead burden of children. Nevertheless, lead poisoning in children has not disappeared and today lead-based paint remains the major source of lead exposure. Furthermore, lead intoxication is a major concern in developing countries.

Neurotoxicity

Central and peripheral nervous system disorders due to lead exposure are well known, including lead encephalopathy and neuropathy, but there has been increasing concern regarding subclinical neurologic disturbances, especially in children, at low levels of lead exposure. Several studies tended to support the hypothesis that low levels of blood lead, well below 25 μg/dl, may induce neurobehavioural, cognitive, developmental and biochemical abnormalities [76]. It is difficult to determine exactly the threshold value for lead neurotoxicity, especially because of inter-individual susceptibility and the role of associated factors, such as obstetrical parameters, chronic diseases, nutritional deficiency or concomitant exposure to other neurotoxic chemicals, for example pesticides, which may potentiate the neurologic effects of lead [75]. Nevertheless, numerous cross-sectional studies as well as prospective studies and

several meta-analyses demonstrated a direct link between low-level lead exposure during the early development, and neurobehavioral and cognitive impairment and intelligence quotient deficit becoming evident later in childhood through adolescence. These were observed with levels as low as 10 μg/dl [77]. On the basis of these results, it was concluded that blood lead concentrations of 10–15 μg/dl are of concern regarding the adverse effects of lead on the neurobehavioural development of children; the Center for Disease Control lowered the current level for childhood lead poisoning, from 25 μg/dl to 10 μg/dl [78]. Recently, Rosen [77] showed that cognitive impairment may decline after cessation of exposure, and that changes in cognitive performance were significantly related to decreases in blood lead levels.

Nephrotoxicity

N-acetyl-β-D-glucosaminidase was shown to be the earliest marker of renal injury in lead-exposed workers, and it seemed to be more sensitive than retinol binding protein, despite a weak dose-effect relation with blood lead levels [79]. The underlying mechanism for the increase in N-acetyl-β-D-glucosaminidase remains to be elucidated. Another study of several possible markers of lead-induced nephrotoxicity was conducted in 50 workers moderately exposed to lead (blood lead concentrations above 35 μg/dl and duration of exposure of one year at least). The only significant findings were an increase in the mean urinary excretion of thromboxane (TXB_2), N-acetyl-β-D-glucosaminidase and sialic acid, and a decrease in 6-keto-$PGF_{1\alpha}$. The urinary excretion of tubular antigens was also positively associated with the duration of exposure [80]. The clinical relevance of these biochemical changes is still unknown. A later study suggested that these biochemical changes are not associated with deleterious effects on the renal hemodynamics, since the capacity of the kidney to increase the glomerular filtration rate (creatinine clearance) after an oral protein load (consumption of 400 g of cooked red meat), was similar in both lead workers and controls [81]. Thus, early biomarkers of lead-induced nephrotoxicity are far less documented than for cadmium, and require further study.

Treatment

$CaNa_2EDTA$ was introduced more than 20 years ago to treat lead poisoning, alone or in combination with BAL. When given promptly, it was shown to be effective in preventing the progression of symptomatic intoxication and in normalizing the biochemical indices of lead poisoning. However, its effects in asymptomatic poisonings, and especially its efficacy in the prevention or modification of neurotoxicity, is unknown. In particular, $CaNa_2EDTA$ appeared to be ineffective on the mobilization of lead in bones [72].

Recently, DMSA was developed as an orally active chelating agent for the treatment of lead and other heavy metal poisonings in both children and adults. DMSA is a relatively specific chelator with little chelating action on essential

trace elements. It was shown to lower blood lead rapidly, increase urinary lead elimination and restore the metabolic activity of the heme biosynthetic pathway in children and in adults with blood lead levels ranging from 30 to 100 μg/dl [82]. It seems to be a relatively safe drug with adverse effects including mild gastrointestinal upset, elevated serum transaminases, and neutropenia [83], even though data are not sufficient to exclude more serious events. DMSA was recently approved by the US FDA for treating lead-poisoned children with blood lead levels exceeding 45 μg/dl. Because DMSA chelates lead from soft tissues, including the brain, in animals, it was hoped that it could be an effective drug on neurobehavioural deficits induced by lead, but this has not yet been confirmed. Thus, DMSA has rapidly appeared as an important challenge for the coming years, requiring further clinical research to assess its safety and to compare its efficacy on cognitive and neurobehavioural changes with other therapeutics.

NICKEL

Nickel is an ubiquitous metal known since 1751. There are many sources of exposure, especially in the home and at the work place. Nickel is widespread in cheap jewellery and clothing accessories. The main use of nickel is the manufacture of stainless steel, but the production of alloys providing strength and corrosion resistance, foundry, or for electroplating or the non ferrous industry, are other major industrial activities involving nickel. Nickel salts are used as antiknock agents, antioxidants, catalysts and pigments. Nickel is the fourth most used metal in the world and the annual consumption is estimated to be over 670,000 tons [84]. Nickel is a recognized carcinogen, mainly nickel sulfate and combinations of nickel sulfides and oxides encountered in the nickel refining industry, and it is a powerful sensitizer. Nickel carbonyl which is used in the refining process of nickel to obtain a very pure metal, and as a catalyst in the petroleum, plastic and rubber industry, is highly toxic.

Nickel allergy

Nickel is the commonest cause of contact dermatitis. Eczema is the usual form of contact allergy, but urticaria, polymorphous erythema or vasculitis may also occur. The prevalence of nickel allergy in the general population is 8–10%. Women are more affected and the sensitization seems to become more frequent and to occur earlier in life. Nickel is the most common allergen found in pediatric contact dermatitis. Contact dermatitis is related to the wear of clothing accessories and cheap jewellery containing nickel, particularly earrings. Women with pierced ears are four to five times more likely to present with a positive patch test to nickel. Contact dermatitis may also occur in the occupational setting, and various categories of workers may have contact with nickel, for example, auto mechanics, cashiers, catalyst makers, ceramics workers, dyers, electronic workers, electroplaters, hairdressers, ink makers, jewellers [13].

Due to the widespread use of nickel in the indoor environment, it is difficult to assess the role of occupation in the induction of dermatitis. The mechanism of nickel-induced contact dermatitis is delayed allergy. Nickel ions readily penetrate the skin and are presented to the immune system by the Langerhans cells. After a first contact with nickel, circulating nickel-specific T cells, presumably produced in the paracortical areas of the regional lymph nodes, react with the metal on each subsequent contact. Nickel sensitivity is diagnosed by occluded patch test with 5% nickel sulfate, read after 72 hours.

In recent years, several authors have focused on nickel-induced systemic allergy. This was based on the assumption that contact allergy may be maintained by nickel in food, or that skin eruption may occur far from the contact site [85]. Cases of immediate allergy with rhinitis and asthma have also been reported, although rarely [86].

Nickel carcinogenicity

Nickel carbonyl was discovered at the beginning of this century as a means to obtain very pure nickel. Nickel–copper sulphide ore is treated by roasting to produce oxides which are then exposed to sulfuric acid with the resulting formation of copper sulphate and impure nickel as residues. The impure nickel is reduced in the presence of a hydrogen-rich gas and then exposed to carbon monoxide at room temperature to produce nickel carbonyl. The gas is passed over heated nickel where it decomposes, resulting in the production of very pure nickel.

After several years, this process was shown to induce nasal and lung cancers. Over 80 cases of nasal cancer were reported and the rate of lung cancer was found to be more than four times higher than in the general population. Dusts of impure sulphides and oxides were thought to be involved, but the possible role of arsenic as an impurity in sulphuric acid was also discussed. Worldwide restrictions on this process have been imposed because of carcinogenicity, and the risk was considered to be virtually eliminated by the late 1930s [84]. Similar problems have occurred in countries (e.g Canada, Norway and Russia) refining sulphide ores by high temperature roasting [87].

The International Committee of Nickel Carcinogenesis in Man [88] re-analysed all previous studies and concluded that different forms of nickel may give rise to lung and nasal cancer. The exact cause of nickel carcinogenicity is not totally clear, but it was thought to involve mainly exposure to a mixture of oxidic and sulfidic nickel at high concentrations. Exposure to large amounts of oxidic nickel alone was also associated with lung and nasal cancers. Soluble forms of nickel, like chloride or nitric nickel, were also proposed as increasing the risk of cancer and enhancing the carcinogenic action of less soluble forms, such as oxidic or hydroxidic nickel [88]. Nowadays, there is no evidence of the possible carcinogenic effect of metallic nickel and nickel alloys in humans [87]. The involvement of nickel in the development of other cancers has not been yet established.

Nickel carbonyl

Since the development of occupational safety standards to prevent and limit exposure to nickel carbonyl, acute poisonings have been rare, but potentially highly severe [89]. Accidental acute exposure to nickel carbonyl occurs via inhalation. The toxicity of nickel carbonyl has been compared to that of hydrogen cyanide. Immediate effects include mild and transient changes with vertigo, headache, weakness and chest pain. Nausea, vomiting and cough may be also noted. Severe delayed effects may appear after an asymptomatic period of a few hours or days, including chest pain, cough, tachypnea, dyspnea, cyanosis, weakness, arrhythmias. The primary target organ of nickel carbonyl toxicity is the lung, with pulmonary edema and hemorrhage. Hyperglycemia, hepatic and renal damage are less common. Death usually results from respiratory failure, myocarditis, and cerebral edema or hemorrhage. The mechanism of the tissue toxicity of nickel carbonyl is not completely elucidated, but could involve the inhibition of ribonucleic acid synthesis.

Dithiocarb appeared to be the most successful chelating agent for acute nickel carbonyl intoxication. It increases the excretion of nickel in the urine and the feces. Disulfiram, an antabuse drug, is metabolized to two molecules of dithiocarb and has been successfully used to treat nickel dermatitis [90].

ZINC

Zinc is a trace element essential for life; zinc deficiency may induce impairment in growth, fertility and immune competence. Zinc is necessary for the activity of metallo-enzymes and acts as an intracellular calcium blocker.

The acute inhalation of fumes containing high concentrations of zinc oxide during welding, may induce a lung reaction called "metal fume fever", characterized by general symptoms and malaise [91]. Several zinc salts, like zinc chloride, sulfate and gluconate, have local corrosive effects.

Acute poisoning has been rarely described following deliberate self-ingestion of zinc phosphide used as a rodonticide. Toxicity occurs through the generation of phosphine gas which is highly toxic. Early symptoms of toxicity include dizziness and headache, nausea, vomiting and dyspnea. Immediate death may occur from pulmonary edema. A total ingested dose of 4 g is usually considered to be lethal, but survivors were reported after a total dose of 50 g [92]. Treatment is mainly symptomatic. The role of chelation in acute zinc ingestion remains unclear [93].

TIN

Tin was considered as a precious metal and is used to produce bronze, the tin–copper alloy. Tin and its inorganic and organic derivatives are also used in the industry to manufacture containers for food and liquids, electrical and engineering components, stabilizers in plastics, as medicines (tin oxide and

stannous chloride are used as antihelmintics) and in the agriculture (various organic compounds are used as molluscicides, fungicides, insecticides and miticides).

Tin and inorganic tin derivatives have a low toxicity. Several tin salts, particularly tin chloride, have corrosive local effects. The inhalation of fumes or dusts containing high amounts of tin may result in irritation of the respiratory tract. The inhalation of tin oxide fumes may cause metal fume fever, with pyrexia, myalgia, tracheo-bronchitis and eventually fatal pneumonia following massive exposure. Many cases of tin-induced pneumoconiosis, or stannosis, have been reported following the chronic inhalation of tin oxide.

Organo-tin compounds have a higher systemic toxicity, especially trimethyltin and triethyltin, which are well absorbed from the gastrointestinal tract. The main toxic effect is neurotoxicity. Triethyltin was shown to induce intramyelin edema and the hippocampus is a target of trimethyltin neurotoxicity in animals [94]. In 1954, an epidemic of organo-tin poisonings was caused, mainly in France, by the ingestion of a medicinal formulation recommended for the treatment of furunculosis, osteomyelitis, anthrax and acne. The formulation contained di-iododiethyltin contaminated with triethyltin iodide. Two hundred and ten cases of poisonings were reported with 102 deaths. Symptoms included headache, nausea, vomiting, equilibrium disturbances, coma and death [95]. Death resulted from cardiac or respiratory failure, or from convulsions and coma due to increased intracranial pressure. Sequels such as persistent headache and asthenia were often reported.

Organo-tin compounds have been shown to be markedly immunotoxic, particularly in rats with thymic atrophy as the earliest evidence of toxicity. However, it is not known whether immunotoxicity can occur in man.

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20. Insecticides

SYNTHETIC PYRETHROID INSECTICIDES

Pyrethrum is an insecticide extracted from the dried flowerheads of *chrysanthemum cinerariae folium* and other species. There are six known insecticidally active compounds in pyrethrum (pyrethrin I & II, cinerin I & II, and jasmolin I & II). Modifications to the chemical structures of these natural pyrethroids (pyrethrins) have produced a number of synthetic pyrethroids with improved physical and chemical properties to enhance stability in the natural environment and to produce greater biological activity [1].

Many commercially available synthetic pyrethroids have been specifically developed for the control of both household and agricultural insects. They are also used to control human lice. Pyrethroids available to date include allethrin, biphenate, cyflutrin, cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, fenvalerate, flucythrinate, fluvalinate, furamethrin, kadethrin, lamdacyhalothrin, permethrin, d-phenothrin, resmethrin, tefluthrin, tellallethrin, tetramethrin, and tralomethrin [2].

Formulations include aerosol sprays, smoke coils, electric mats, oil formulations, emulsifiable concentrates and wettable and dustable powders. A shampoo and lotion formulation is also available for the control of human lice. The formulated products often combine the synthetic pyrethroids with a synergist, such as piperonyl butoxide, for increased insecticidal activity and may also contain other insecticides [2].

Pyrethroids, like most other insecticides, interfere with the function of the nervous system. They act on the axons in the peripheral and central nervous systems by interacting with sodium channels in mammals and insects [3,4]. On the basis of electrophysiological studies with peripheral nerve preparations of frogs, it is possible to distinguish between two classes of pyrethroid insecticides (Type I and II). A similar distinction between these two classes has been made on the basis of the symptoms of toxicity in mammals and insects [2].

Pyrethroids without an α-cyanosubstituent, generally fall into type I (e.g. allethrin, bromophenethrin, cismethrin, and permethrin), and cause a moderate prolongation of the transient increase in sodium permeability of the nerve membrane during excitation [5]. This results in relatively short trains of

repetitive nerve impulses in sense organs, sensory nerve fibres, and, in effect, nerve terminals. Poisoning in mammals closely resembles that from DDT. It involves a progressive development of fine whole-body tremor, exaggerated startle response, uncoordinated twitching of the dorsal muscles, hyperexcitability and death. Metabolic exhaustion and hyperthermia is the usual cause of death [6].

Type II pyrethroids include most of the pyrethroids that contain an α-cyano group, for example cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, and fenvalerate. These substances cause a long-lasting prolongation of the transient increase in sodium permeability of the nerve membrane during excitation. This results in long-lasting trains of repetitive impulses in sense organs and a frequency-dependent depression of the nerve impulse in nerve fibres [7]. Type II poisoning in rats includes progressive development of nosing and exaggerated jaw opening, salivation, incoordination progressing to a very coarse tremor, choreoform movements of the limbs and tail, choreoathetosis (writhing spasms), tonic seizures, apnoea and death [6].

Intermediate signs of poisoning in animals representing a combination of types I and II are produced by some pyrethroids. These appear to represent a true combination of the I and II classes and thus constitute a transitional class [6].

Human poisoning

Most reports on the adverse effects associated with exposure to pyrethroids have arisen from the occupational setting [8–10]. Early descriptions indicated that pyrethroids caused abnormal sensations of the face and irritative symptoms of the skin and upper respiratory tract [11,12].

Chinese investigators have reported a large number of both occupational and accidental poisonings involving pyrethroids. A 1989 review of 573 cases of acute pyrethroid poisoning reported in the Chinese medical literature (1983–1988) included 325 cases of deltamethrin poisoning (158 occupational cases and 167 accidental), 196 cases of acute fenvalerate poisoning, 45 cases of acute cypermethrin poisoning, and seven cases of other pyrethroid poisoning [9].

A recent report included a cross-sectional survey on the prevalence of pyrethroid poisoning in 3113 Chinese cotton farmers [8]. Adverse effects of pyrethroid exposure were found in 834 of them (26.8%), including abnormal facial sensations, central nervous system and systemic effects. Ten subjects were diagnosed as having mild occupational acute poisoning. Measurements of pyrethroid concentrations in the air of the breathing zone, in skin pads, and in urine samples showed that dermal contamination is the main route of exposure to pyrethroids in cotton growers [10].

From these studies [8–10], it has been shown that the clinical manifestations of acute poisoning induced by the major types of pyrethroids are very similar. Initial symptoms include irritation of the skin and respiratory tract (or digestive tract if ingested). In acute poisoning, abnormalities of nervous excitability

occur. Signs and symptoms may be categorised according to the degree of severity, as follows:

- *Mild*: facial paraesthesias, contact dermatitis, dizziness, headache, transient changes in EEG, anorexia, nausea, vomiting and fatigue.
- *Moderate*: mild disturbance of consciousness, muscular fasciculations in the limbs.
- *Severe*: convulsions, pulmonary oedema, coma.

The onset of these symptoms varies, and depends upon factors such as the route of absorption and quantity involved. In patients with occupational poisoning, skin symptoms usually develop within 4–6 hours after exposure, with systemic symptoms occurring as late as 48 hours post-exposure. Paresthesia of the facial skin can develop approximately 30 minutes post-exposure and does not usually last beyond 24 hours from the termination of exposure [12,13]. Following ingestion, the initial symptoms involve the gastrointestinal tract, developing 10–60 minutes after exposure. Additionally, immunological reactions including sudden bronchospasm, oro-laryngeal oedema, hypersensitivity pneumonitis and anaphylaxis have been reported.

Management of poisoning

Pyrethroid plasma and urine levels are not considered to be clinically useful except, perhaps, to confirm a diagnosis. A gas chromatographic technique suitable for this purpose has recently been described [14]. The prognosis of acute pyrethroid poisoning is found to be good following appropriate management. Treatment is essentially symptomatic and supportive following appropriate decontamination measures to prevent further absorption of the pesticide. These may involve irrigating the skin and eyes with copious amounts of water for 10–15 minutes, emesis, gastric lavage, and activated charcoal as a slurry that usually includes a cathartic [9].

The skin irritation and paraesthesia following dermal exposure have been shown to be alleviated by topical vitamin E cream [15]. Considerable relief may also be obtained by the use of lipophilic agents such as corn oil or white soft paraffin [16].

Seizures are the most severe clinical sign of toxicity, and control with intravenous diazepam is recommended. Atropine has been shown to be useful in relieving salivation, diarrhoea and pulmonary oedema. The smell of pyrethroid emulsifiable concentrate formulations has been reported to be similar to that of organophosphate pesticides, and in some cases have been misdiagnosed on this basis together with the presenting symptoms of muscular fasciculation and pulmonary oedema. To differentiate between these two types of insecticide poisonings the exposure history and response to the administration of atropine (usually less than 10 mg is tolerated in the absence of depressed cholinesterase) should be considered [9]. However, it should be noted that some pyrethroid insecticides are co-formulated with organophosphates, which complicates the clinical picture.

ORGANOPHOSPHATE INSECTICIDES

Organophosphate insecticides are normally esters, amides or thiol derivatives of phosphoric, phosphonic, phosphorothioic or phosphonothioic acids. More than 100 anticholinesterase organophosphate insecticides are known [17].

They can be absorbed by all routes including inhalation, ingestion, and dermal absorption. The toxicological effects of the organophosphate insecticides are almost entirely due to the inhibition of acetylcholinesterase in the nervous system. A few organophosphoate insecticides have produced delayed and persistent peripheral neuropathy, apparently unrelated to cholinesterase inhibition. Toxicity may also be due to the effects of solvent vehicles or other components of formulated insecticides.

Human poisoning

The signs and symptoms of organophosphate poisoning are an expression of the effects caused by excess acetylcholine; they may occur in various combinations and can be manifest at different times. Signs and symptoms can be summarised into three groups: muscarinic, nicotinic, and central nervous system effects.

According to the degree of severity of poisoning, the following signs and symptoms can occur [6,17–19]:

- *Mild*: anorexia, headache, dizziness, weakness, anxiety, substernal discomfort, tremors of the tongue and eyelids, miosis, and impairment of visual acuity.
- *Moderate:* nausea, salivation, tearing, abdominal cramps, vomiting, sweating, slow pulse, and muscular fasciculations.
- *Severe:* diarrhoea, pin-point and non-reactive pupils, respiratory difficulty, pulmonary oedema, cyanosis, loss of sphincter control, convulsions, coma, and heartblock. Hypoglycemia and acute pancreatitis have occurred.

A few organophosphate insecticides (for example, mipafox, leptophos, merphos, trichlorphon, chlorpyrifos) have produced delayed and persistent peripheral neuropathy, apparently unrelated to anticholinesterase action [6]. In human exposures, the delay may be up to four weeks after the first exposure. The first symptoms are often sensory with tingling and burning sensation in the limb extremities followed by weakness in the lower limbs and ataxia. This progresses to a paralysis, which, in severe cases, affects the upper limbs also. Children are less severely affected than adults, but recovery is slow and seldom complete in adults; with the passage of time the clinical picture change from a flaccid to a spastic type of paralysis [17].

Electromyographic studies may be used to confirm distal neuropathies and have helped with the understanding of the functional basis of this clinical manifestation. Changes have been associated with a demonstrable depression

of plasma or red cell cholinesterases, and are manifest as alterations in psychomotor performance, memory, speech and mood, with features of depression, anxiety and irritability [19]. Less commonly encountered are neurological symptoms such as chorea and psychiatric disturbances including psychoses and depression [20].

Additional neurological investigations may be helpful in elucidating cerebral disturbances: electroencephalographic changes have been noted to occur in organophosphate poisoning and have been considered to represent a specific effect on the mid-brain [21]; computerised cerebral tomography may be of use in the diagnosis and follow-up by cholinesterase inhibitors, as generalised cerebral atrophy has been demonstrated [22]. A recent case-controlled study of neuropsychological performance was conducted on agricultural workers in Nicaragua who had been admitted to hospital between 1986–1988 for occupationally-related organophosphate poisoning. A significant decrease in neuropsychological performance amongst these individuals compared with controls was demonstrated. The authors concluded that even single episodes of clinically significant organophosphate poisoning are associated with a persistent decline in neuropsychological function [23].

A syndrome following the treatment and resolution of the cholinergic signs of organophosphate poisoning has been described. As this occurred before the late effects of organophosphates it has been called the intermediate syndrome [24]. The syndrome consists of a proximal limb paralysis starting one to four days after poisoning. The course is not influenced by atropine or oximes and, as the respiratory muscles are affected, respiratory support is necessary. Although other case reports have been published since this observation, it is not clear whether they represent a unique clinical entity [25].

Management of poisoning

Cholinesterase levels are helpful in securing a diagnosis of organophosphate insecticide poisoning, but have no relation to management. While the red cell cholinesterase level is a more accurate assessment of poisoning, most hospital laboratories perform the serum cholinesterase level, which measures pseudocholinesterase found in the liver and the serum. A favourable response to atropine is a more reliable diagnostic aid than any cholinesterase assay since treatment must often be initiated before any laboratory results are available [17].

It has been estimated that the coefficient of variation for acetylcholinesterase activity in samples from an individual is 8–11%, and that a decrease of 23% below pre-exposure level may, therefore, be considered significant. Depressions of 25% or more are considered indicators for removal of an exposed individual from further exposure to pesticides until levels return to normal [17]. Recovery of enzyme function, together with an improving clinical picture, is used as a guideline as to when to terminate treatment with atropine and pralidoxime in the more severe cases of poisoning. Interpretation of differential analysis of the plasma and red cell enzymes is, however, complicated by the

finding that various organophosphate insecticides will inhibit one or other enzyme selectively [19]. In addition, other influences such as genetic, pathological, and pharmacological factors must be considered when interpreting results [26].

The management of organophosphate poisoning should be primarily directed to decontamination and resuscitation. Decontamination is vital in reducing the dose of organophosphate absorbed by the patient, but care must be taken not to contaminate others, such as medical and paramedical workers. Solvent vehicles and other components of the formulated organophosphate insecticide may complicate the clinical picture and should be considered [6].

Supportive measures should be directed towards the cardiorespiratory system with particular emphasis on maintenance of cardiac rhythm, blood pressure and respiratory rate; the removal by suction, of respiratory and oral secretions which may cause respiratory distress; and the oxygenation of the patient. Respiratory arrest may be a feature of organophosphate poisoning [19]. When artificial ventilation is required and a paralysing agent is needed, the ganglion blocker, suxamethonium, is to be avoided as undue sensitivity to this agent may lead to prolonged respiratory paralysis [27]. Suxamethonium is normally rapidly metabolised by pseudocholinesterase; hence an alternative neuromuscular blocking agent should be used. Phenothiazines and antihistamines are also contraindicated since they have anticholinesterase activity and may potentiate organophosphate insecticide toxicity. Central nervous system depressants (e.g. opiates) should also be avoided since they may increase the likelihood of respiratory arrest [18].

Ingested organophosphates should be removed by early gastric lavage, with protection of the airway if necessary, and this may be the best remedy in unconscious patients. Gastric lavage is most effective within thirty minutes of ingestion, as organophosphates are rapidly absorbed from the gastrointestinal tract. Hence, the use of syrup of ipecac as an emetic is controversial since vomiting is often delayed and additionally, Ipecac may be contraindicated in the case of insecticides dissolved in hydrocarbon solvents. Administration of oral activated charcoal and a cathartic, in conventional doses, may also be considered for the reduction of further absorption [17,28]. If poisoning has occurred by inhalation, the individual should be removed from the source of exposure and given oxygen, the rescuer taking adequate precautions.

Dermal exposure may be managed by removal and discarding of contaminated clothing (particularly leather which absorbs pesticides) into sealed bags and repeated vigorous washing of exposed skin with soap and copious warm water. Delayed inadequate washing with ordinary soap and water was shown by Fredrikkson [29] to remove only 50–70% of radiolabelled parathion. Special attention should be given to washing in skin creases, around the ears, and the external auditory canals, around the umbilicus and genitalia, and under the nails.

Ocular contamination should be managed by continuous irrigation of the affected eye with clean, luke-warm water for 15 minutes. Contact lenses should be removed before irrigating with water.

Depending on the severity, organophosphate poisoning can be treated with [6,17–19]:

- atropine, which is the antidote of choice and is useful in reversing the muscarinic features;
- oximes, which reactivate cholinesterases inhibited by organophosphate insecticides.

Atropine acts as a physiological antidote by competitively blocking the action of acetylcholine at muscarinic receptors, and will reverse the excessive parasympathetic stimulation which results from acetylcholinesterase inhibition. A trial dose of atropine should be instituted on clinical grounds when one suspects organophosphate insecticide poisoning. The ability to administer large doses of atropine without observable adverse effect is virtually diagnostic of organophosphate poisoning.

Oxime reactivators (e.g. pralidoxime and obidoxime) specifically restore cholinesterase activity. The treatment should be administered within 24–48 hours of poisoning since it is considered to be ineffective as an antidote once "ageing" of phosphorylated cholinesterase enzyme with irreversible loss of function has occurred. The timing of administration, however, is controversial. If absorption, distribution, and metabolism are thought to be delayed for any reasons, oximes can be administered for several days after poisoning. Effective treatment with oximes reduces the required dose of atropine. Pralidoxime (as the chloride or mesylate) is the most widely available oxime [30]. The iodide salt of pralidoxime should no longer be employed because of the risk of iodism and cardiac arrest.

The optimum dosage and regimen for the treatment period of poisoning by individual organophosphate insecticides has not been clearly defined. The purpose of oxime therapy is to enhance the spontaneous reactivation of phosphorylated acetylcholinesterase to acetylcholinesterase so that some activity remains present at vital sites. It is therefore imperative that oximes be used regularly throughout the treatment period. The time after the onset of organophosphate toxicity at which oxime therapy may still be useful (24–48 hours) is derived from the half-lives of ageing of enzymes of particular organophosphate insecticides [6]. However, on theoretical grounds, there may be value in initiating oxime therapy for up to 1–2 weeks after onset of toxicity in the case of diethyl-organophosphates. This is also particularly relevant for organophosphates which are stored in adipose tissue and subsequently released over a period of time. These areas require further elucidation.

Obidoxime is not yet widely available, clinical experience is limited and, as with pralidoxime, further research into the optimal dose and regimen is required [19].

Very little is known regarding the optimum dose and pharmacokinetics of atropine in relation to the dose of pralidoxime, the severity of the organophosphate insecticide poisoning, and the properties of a particular organophosphate.

CARBAMATE INSECTICIDES

These are carbamate ester derivatives and more than 60 insecticides are known [31]. The carbamate insecticides are reversible cholinesterase inhibitors. They are absorbed by all routes including inhalation, ingestion and dermal absorption. Their general lack of solubility in lipids makes them less toxic via the dermal route than by other routes.

Human poisoning

Symptoms and signs are similar to those of organophosphate poisoning, i.e. visual disturbances, gastrointestinal hyperreactivity, and respiratory difficulty due to the anticholinesterase effect. Penetration into the CNS is very much less than with organophosphates, though convulsions may occur in massive overdoses and indicate a poor prognosis as does respiratory depression, which is the usual cause of death [6,31].

Management of poisoning

Treatment of poisoning by anticholinesterase carbamates is similar to that of organophosphorus compounds, with the exception of oximes. The use of oxime reactivators of inhibited cholinesterase enzymes in carbamate poisonings has received mixed review in the medical literature. Conventional therapy recommends atropine as the treatment of choice with pralidoxime administered only when atropine has first proven inadequate, in serious mixed poisonings with both carbamate and organophosphorus compounds, or in serious poisonings by unidentified cholinesterase inhibitors. However, data have been limited to animal toxicity studies [32–36], and there is no reported evidence in humans that pralidoxime is unsafe as adjunctive therapy in a critically-ill patient poisoned by a carbamate [6,37]. Further research into the role of pralidoxime as an adjunct in the management of carbamate poisoning is warranted. Diazepam is recommended in moderate or severe cases to relieve anxiety and because it may counteract some CNS-related symptoms not affected by atropine [31].

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21. Herbicides

INTRODUCTION

Herbicides are chemicals used to kill or damage unwanted plants or parts of them. The term derives from the Latin words *herbs* and *caedo*, meaning plant-killer. Since the early observation in 1895-1897 of the selective herbicidal properties of copper sulphate against *Sinapis arvensis* [1], many chemicals have been used or tested as weed-killers. Among these are sulphuric acid, sodium chlorate, borate and arsenite, arsenic trioxide and dinitro-orthocresol. In the middle and late 1930s a growing interest in developing selective herbicidal properties stimulated research for new compounds, leading to the introduction, a few years later, of a class of effective chemicals, the phenoxyacids. In the 1950s another group of compounds, the triazines, with selective herbicidal properties and a much lower acute toxicity than that of phenoxyacids, was developed. In 1962 paraquat, the first of an important class of non-selective contact herbicides, the bipyridylium compounds, was introduced.

In the last decades the production and use of modern herbicides has increased faster than those of any other class of pesticides. The world production of herbicides is more than double that of all insecticides, and more than triple that of fungicides. Modern herbicides can be classified by different criteria such as the chemical class, the time or site of application, the effect on the plant, the mechanism of action or toxicity. The main categories of herbicides in use today, with some examples including both chemical and common names, are listed in Table 21.1. The mechanism of toxicity and main target organs (when known) are presented in Table 21.2.

In this chapter, the known acute and chronic toxicological effects in humans of the major classes of herbicides will be reviewed. When appropriate, current knowledge on the toxicokinetics, toxicodynamics, mechanism of toxicity and target organ(s) of these chemicals will be shortly addressed. Attention will also be paid to that information from animal studies which is particularly relevant to the risk assessment of the long-term human exposure to low concentrations of herbicides.

Class	Chemical name	Common name
Chlorophenoxy acids	2,4-dichlorophenoxyacetic acid	2,4-D
	2,4,5-trichlorophenoxyacetic acid	2,4,5-T
	2-methyl-4-chloro-phenoxyacetic acid	MCPA
	2-methyl-4-chloro-phenoxypropionic acid	MCPP
	2-(2,4,5-trichlorophenoxy)propionic acid	Silvex
Other organic acids	3,6-dichloro-2-metoxybenzoic acid	Dicamba
	trichloroacetic acid	TCA
Amides	N-methoxymethyl-2',6'-diethyl-2-chloro-acetanilide	Alachlor
	N-3,4-dichlorophenyl)propanamide	Propanil
Thiocarbamates	S-ethylcyclohexylethylthiocarbamate	Cycloate
	S-ethyl N,N-hexamethylenethiocarbamate	Molinate
Diphenyl ethers	2,4-dichloro-1-(4-nitrophenoxy)benzene	Nitrofen
Bipyridilium compounds	1,1'-dimethyl-4,4'-bipyridilium ion	Paraquat
	1,1'-ethylene-2,2'-bipyridilium ion	Diquat
Triazines	2-chloro-4-ethylamino-6-isopropylamine-triazine	Atrazine
	2-chloro-4,6-bis(isopropylamino)-triazine	Propazine

Table 21.1. *Chemical class and name of some common herbicides*

Herbicide	Mechanism of toxicity	Target organ(s)
Paraquat	Oxygen free radicals formation (NADPH depletion? lipid peroxidation?)	lung
2,4-D and 2,4,5-T	Largely unknown	CNS, PNS, muscles, lymphoid tissue (kidney?)
TCDD	Bioactivation to reactive metabolites by cytochrome P-450	skin, liver, lymphoid tissue
OP and Carbamates	Acetylcholinesterase inhibition	nervous system (GI tract?)
Amides	Unknown	skin
Atrazine	Unknown	(endocrine system?)

Table 21.2. *Mechanism of toxicity and target organ(s) of some herbicides or their contaminants in mammals*

CHLOROPHENOXY ACIDS

This class of compounds acts on plants by mimicking the action of natural auxins, i.e by altering normal growth and interfering with the transport of nutrients. They are mainly used to destroy broadleaf weeds and grass species in cereal crops and to control plants alongside motorways. The mechanism of toxicity in animals has not been yet clarified, but is probably not mediated by hormonal effects.

Information on the human toxicity of chlorophenoxy herbicides mostly derives from occupational medicine. In many studies and reports, workers were acutely or chronically exposed to one or several chemicals at the same time. A few cases of acute poisoning by accidental or voluntary ingestion of pure 2,4-dichlorophenoxyacetic acid (2,4-D) and/or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) have been described, however. In these cases, the chlorophenoxy acids showed low to moderate acute toxicity and caused local irritation and burning of the skin and mucosae, muscle dysfunction and weakness, hypotension, arrhythmia and respiratory difficulty. An oral lethal dose in humans of more than 6 g has been estimated for 2,4-D [2]. The pharmacokinetics of chlorophenoxy acids have been reviewed recently [3]. Treatment of acute poisonings by phenoxy herbicides includes antiarrhythmic drugs, alkaline diuresis and symptomatic treatment [4].

A number of epidemiological studies have shown a higher tumour-related mortality in subjects exposed to phenoxy herbicides. In a follow-up study on workers exposed to a number of herbicides, Axelson et al. [5] found an excess number of cancers in workers exposed to phenoxy herbicides and/or amitrole. Moreover, early case-control studies [6–8] suggested a possible association between exposure to chlorophenoxy herbicides and soft tissue sarcomas or non-Hodgkin's lymphoma. Such an association has been confirmed by some, but not all subsequent studies [9–12]. Recent reevaluations of the case-control and cohort epidemiology studies, however, have not confirmed a causal relationship between exposure to these herbicides and cancer [13,14]. These and other aspects of 2,4-D toxicology have been reviewed by WHO [15] and IARC [16,17].

During the production or combustion of these chemicals, a number of highly toxic contaminants known as dioxins are produced. Indeed, most toxicological effects of 2,4,5-T have been attributed to the presence of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the toxicologically most potent compound of this group, present as a contaminant in the production of 2,4,5-T and, also, chlorophenols and chlorobenzenes. Several reviews on human exposure and toxicological effects of TCDD in animals and humans are available [18–22]. In experimental animals, TCDD is hepatotoxic, hepatocarcinogenic, porphyrogenic, teratogenic, foetotoxic and immunosuppressive. Acute toxicity of TCDD is largely species-dependent, the guinea pig being the most and the hamster the least sensitive species.

Human absorption of TCDD may occur through the skin and through ingestion. This compound is not water soluble and therefore is unlikely to contaminate the drinking water system but it is greatly bioaccumulated. Pharmacokinetic studies in a human volunteer given an oral dose of ^{3}H-TCDD showed significant (>87%) absorption by the intestine and an elimination half-life of more than a year [23]. The most important effects of TCDD in humans are hepatotoxicity, porphyria and chloracne. The latter is a partially reversible, eruptive lesion of the skin characterized by early erythema and edema, mainly of the face and the neck, followed by follicular hyperkeratosis,

pigmentation and scarring. Hypercholesterolemia, liver disfunction, polyneuropathy, skin hyperpigmentation and hirsutism have also been reported occasionally as a result of human exposure to TCDD. The most important and recent accident resulting in acute non-occupational exposure to TCDD occurred in Seveso, Italy in 1976, when a cloud of 2,4,5-T containing a few kilograms of TCDD was released from an overheated reactor. Several cases of chloracne with other symptoms and biochemical serum alterations were reported [24].

TRIAZINES

Triazine herbicides were introduced in the 1950s and now represent a very large part of the herbicide market throughout the world. Atrazine, a selective herbicide and the most widely used compound of the group, has a low acute oral toxicity in experimental animals (oral LD_{50}: 2 g/kg in the rat). In a long-term carcinogenicity study in rats, however, the compound induced mammary tumours in males and uterine adenocarcinomas and leukemias and lymphomas in females. High doses of simazine, a closely related compound, produced mammary tumours in the same strain of rats as atrazine. Atrazine and simazine are not mutagenic, though, in rats or other animal species, nor *in vitro*. The increased incidence of tumours observed in animals is considered to be hormone-dependent and due to the effects of atrazine on the hypothalamic–pituitary system. Seven epidemiological carcinogenicity studies on triazines were evaluated by IARC recently [25]. It was concluded that exposure to triazine herbicides may be carcinogenic to humans, although the specific role of individual compounds could not be evaluated.

As to the acute or chronic toxicity of triazines in humans, no reports of systemic poisoning by atrazine or simazine have been found in the literature. Only occasional episodes of eye irritation have been reported with atrazine. The chemical is persistent in the soil and in water for months or even years and significant concentrations (>1 μg/l) were recently found in several wellwater supplies in several European countries. This has raised some concern among the general public for possible chronic adverse effects and has led to severe restrictions in the use of this herbicide. Apart from dermal changes, however, no significant chronic effects of triazine herbicides on humans have been reported.

Amitrole, a non-selective herbicide of this group, has an even lower acute toxicity than atrazine or simazine, with an oral LD_{50} in rats and mice of 24 and 15 g/kg body weight, respectively. At high doses, the compound has antithyroid properties in experimental animals and induced thyroid and liver tumours in rats and mice.

BIPYRIDYLIUM COMPOUNDS

Bipyridylium compounds represent a toxicologically very interesting class of herbicides. Paraquat, by far the best known of this group, is an effective, non-selective, contact herbicide that soon after its introduction in the market

attracted much attention for the unique and organ-specific toxicity observed in man after accidental or intentional ingestion. The compound is not volatile and is rapidly bound to and degraded by the soil, so that, despite its high solubility in water, it does not leave any significant residue in the water system nor in food. Conditions of human exposure to paraquat resulting in documented toxic effects are almost invariably limited to accidental or voluntary (suicide) ingestion of concentrated solutions of the compound. In a few cases, however, absorption by damaged skin — the compound is poorly absorbed by the intact skin — and subcutaneous or intravenous injection have been reported. Paraquat undergoes partial but relatively rapid absorption by the gut, peak plasma concentration occurring within 2 to 4 h from ingestion [26]. The herbicide is rapidly distributed in most tissues and excreted by the kidney, with mean distribution and elimination half-lives of 5 and 84 h, respectively [27]. Metabolism is remarkably poor and the compound is excreted in the urine largely unchanged.

The biochemistry of paraquat and its toxicology in experimental animals and man have been extensively reviewed over the years [28–30]. The clinical manifestations and prognosis of paraquat poisoning in man are strictly dose-dependent. After a single high oral dose (>40 mg/kg body weight) massive lesions in various organs and tissues are observed and death inevitably occurs within a few hours or days due to multiorgan failure. When even lower doses (20 to 40 mg/kg) are ingested, early symptoms and signs of local mucosal irritation appear in the mouth, oesophagus and stomach, followed by renal failure in a few days. Finally, a typically delayed, often fatal, fibrosis of the lungs develops in about two weeks and death usually occurs after 2–3 weeks by respiratory failure. When lower doses are absorbed (< 20 mg/kg) only reversible, irritative local signs and mild general symptoms are observed [31].

The mechanism of paraquat-induced selective lung toxicity has been extensively investigated both in humans and animals. Various animal species after a single dose of paraquat develop diffuse fibrogenic changes in the lung similar to those observed in man. The organ-specific effects on the lung have been attributed to selective accumulation of paraquat in alveolar cells, through active uptake by a transport system specific for diamines which is present in the membranes of these cells [32]. The biochemical mechanism underlying paraquat toxicity is thought to be the induction of lipid peroxidation and/or the depletion of cellular NADPH due to an excessive formation of superoxide anion radical ($\cdot O_2^-$) and other reactive oxygen species. The redox properties of paraquat underlying the compound's toxicity are also responsible for its herbicidal effects.

The main histopathological changes of the pulmonary parenchyma observed in a typical case of paraquat poisoning are the destruction of alveolar epithelial cells, capillary hemorrhages and pulmonary edema two or three days after ingestion, followed by interstitial fibroblast proliferation, and finally, diffuse fibrosis in about two weeks. Changes in the kidney (tubular degeneration) and in other organs may also be observed, usually at higher doses.

Local chronic effects of paraquat have been described after occupational exposure, usually in sprayers or manufacturers. Systemic poisoning may also occur following dermal absorption of paraquat. Several cases have been reviewed [33]. These include skin hyperpigmentation and hyperkeratosis, nail damage and eye irritation. Nasal and throat irritation may also result from inhalation exposure to aerosols of paraquat solutions.

Although the mechanism of paraquat toxicity is relatively well understood, and several attempts of rational treatment of poisoning have been carried out, no specific antidotic therapy has been convincingly demonstrated. Symptomatic treatment is also largely ineffective. Several methods have been used to prevent the absorption of paraquat or to remove it from the gut or blood: adsorbents, gut lavage, forced diuresis, hemodialysis, hemoperfusion, blood transfusion, plasmapheresis and immunotherapy. Their efficacy, however, is, at best, limited to patients with low-level absorption. Since it was realised that the probability of survival after paraquat poisoning follows typical asymptotic curves, the prognosis of a patient can be predicted rather accurately by a number of methods based on the plasma concentration and the time elapsed from ingestion [26,34,35]. The outcome of paraquat poisoning may also be predicted by measuring the patient's blood arterial gases [36].

Another bipirydilium herbicide, diquat, is also acutely toxic to humans, although with a somewhat lower toxicity than that of paraquat, the human lethal dose being of 0.1–0.2 g/kg body weight [37], a poorer absorption by the gastrointestinal tract accounting for this lower toxicity. Diquat, like paraquat, is reduced to a free radical form which aerobically also undergoes autoxidation and formation of superoxide radicals. Although the biochemical mechanisms of paraquat and diquat toxicity appear to be similar, diquat does not induce the delayed form of toxicity of paraquat. In the relatively few cases of diquat poisonings reported in the literature, acute symptoms are very similar to those typical of paraquat poisonings (e.g. mucous membranes ulceration, gastrointestinal and neurological symptoms, renal failure, respiratory failure), but no proliferative or fibrotic changes were observed in the lung.

CHLOROACETANILIDE COMPOUNDS

The general structure of this class of herbicides is R_1–C(O)–N (R_2,R_3) and the main chemicals of this group are alachlor, metolachlor and propanil. Their acute toxicity in animals is rather low, with oral LD_{50} values in the rat ranging from 1.4 to 2.8 g/kg for propanil and metolachlor, respectively [38]. Skin sensitization has been reported in both experimental animals and humans. The toxicological reevaluation of alachlor raised some concern that long-term human exposure to this herbicide present as a contaminant in well water might incur a significant carcinogenic risk for humans. In various long-term carcinogenicity studies in animals, alachlor was found to induce oncogenic effects in various tissues of rats (nasal turbinates, stomach and thyroid) and mice (lungs). Based on these studies, it was classified by the U.S. Environmental

Protection Agency (EPA) as a probable human carcinogen, corresponding to a category 2B carcinogen in the IARC classification. Alachlor is metabolized in the liver and was found to be hepatotoxic in long-term feeding studies in the rat and the dog. The closely related analogue metolachlor was also found to induce liver and nasal turbinate tumors in rats. Not much is known, however, about the acute and chronic toxicity of these compounds in humans.

ORGANOPHOSPHATES AND CARBAMATES

These compounds represent, together, the single largest group of insecticides currently used throughout the world. A few organophosphate and carbamate compounds have been developed and marketed as herbicides. In contrast with insecticides, however, organophosphate and carbamate herbicides have little if any anticholinesterase activity and, therefore, low or very low acute toxicity in animals. Glyphosate, for instance, has an oral LD_{50} in the rat of 5.6 g/kg body weight, whereas that of the most common carbamate herbicides ranges from 0.5 to 11 g/kg [38].

However, Sawada et al. [39] reported 56 cases of human poisoning, including nine deaths, following the ingestion — mainly voluntary — of an herbicide containing glyphosate. Similarly, Tominack et al. [40] reported 97 telephone consultations on cases of ingestion of glyphosate-containing herbicides of which 11 died. Other authors have published similar findings [41–43]. Severe poisonings, mostly intentional, were associated with gastrointestinal disturbances, marked hypotension, pulmonary edema and renal failure.

Recently, acute poisonings were reported with glufosinate [44,45].

OTHER HERBICIDES

Other classes of herbicides of documented or potential toxicological significance for man include the thio- (molinate, cycloate) and dithiocarbamates, the diphenyl ethers (nitrophen), the nitriles and some heterocyclic compounds. No systemic poisoning has been reported, however, in the literature with thiocarbamate or dithiocarbamate herbicides. Metam, a dithiocarbamate compound, was responsible for contact dermatitis in a worker. Substituted ureas (diuron) may be irritant to the skin and the eye of humans and were found to induce microsomal enzymes in rats. Diphenyl ethers (nitrofen) were also found to be irritant to the skin and the upper respiratory tract. Nitrile herbicides, known uncouplers of oxidative phosphorylation in plants, may have a similar mechanism of toxicity in mammals. A few cases of acute human poisoning following oral or environmental exposure to ioxymil have been reported.

CONCLUSION

Herbicides are valuable chemicals whose agricultural use is likely to continue and, possibly, increase in the near future. Their use in some cases is

associated with a significant toxicological risk for man. A better understanding of the mechanism of toxicity in mammals, however, will improve the toxicological assessment of these chemicals and, together with a more controlled use and a more appropriate perception of the risk, contribute to limit the occurrence of new cases of human toxicity.

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22. Fumigants, fungicides and rodenticides

Undesirable effects that result from the indiscriminate use of agricultural pesticides in developing and developed countries are widespread. Like other chemicals, pesticides can enter the body via the skin, lungs and gastro-intestinal tract. The major form of accidental acute pesticide intoxication is contamination of the skin with subsequent absorption of the pesticide. Liquid formulations, especially those containing organic solvents, may permeate more rapidly than, for example, solid products or those containing water. Skin damage facilitates absorption of chemicals. Direct contact of pesticides with eyes generally causes irritation, pain, excessive lacrimation, and sometimes visual disturbances.

Acute work-related pesticide poisoning is a less frequent cause of admissions for possible poisoning than suicide. Especially in adults, suicide is a much more common reason for severe pesticide intoxications. Generally the exposure routes in occupational intoxications are skin, eyes and lungs, while in suicide attempts the gastro-intestinal tract is the major exposure route.

The choice of the compounds discussed in this chapter is, for example, based on relatively frequently occurring occupational intoxications with a specific compound, a recent change in therapy or a less extensive discussion of the compound in other handbooks. Therefore the attention paid to a certain compound may sometimes be more extensive than at other times or in different publications. Results from animal experiments are only mentioned when new medical toxicological information has become manifest.

FUMIGANTS

Fumigants are gaseous materials or vapours used for the control of insects or rodents in tightly enclosed spaces and for sterilizing soils, and also for the sterilization of grain stores, greenhouses, food stores and warehouses. They are used on grains, milled products, fresh fruit and vegetables, mushrooms, nuts, coffee and cocoa beans. Fumigants should leave no residue, odour, or aftertaste in the treated goods. Highly volatile chemicals used as fumigants include

ethylene oxide, methyl bromide, and phosphine. Some fumigants previously in regular use, for instance carbon disulphide, carbon tetrachloride, chloroform, tetrachloroethylene and trichloroethylene are not considered in this Chapter, because they are for various reasons no longer in frequent use. Fumigants that are suspected carcinogens are gradually being banned or are no longer in use on the food supply [1]. Generally the equipment for sterilizing soils is more advanced and the personnel is sufficiently trained and therefore occupational exposures to fumigants during soil sterilization are infrequent. More occupational exposures occur during applications of a fumigant in enclosed spaces. Re-entry following fumigation is another frequent cause of occupational exposure. It is important to realise that fumigants are generally heavier than air and therefore samples for concentration measurements should be taken at the lower levels in enclosed spaces. Of course when the fumigant is lighter than air the sample should be taken at the higher levels in the fumigated room. Further, it is important to realise that some fumigants may adsorb onto materials and after the fumigation the compound may become available through desorption. Therefore after ventilation of enclosed spaces the room should be closed and for example after 24 hours (depending on the compound and surrounding materials), the concentration of the fumigant should be determined again. Depending on the measured concentration the room can be decontrolled.

Methyl bromide

Methyl bromide (CH_3Br) is commercially available as a liquid with a boiling point of 3.56°C. At normal temperature and pressure it is a colourless and odourless gas. Methyl bromide is denser than air. It is only slightly soluble in water and easily soluble in ethanol, chloroform, ether, etc. [2]. It can penetrate many usually impermeable substances which are often used for protective equipment such as leather, rubber and some plastics.

Methyl bromide is widely used as a disinfectant to fumigate soil [3] and to a lesser extent for fumigating post-harvest foods such as wheat, cereals, spices, nuts, dried foods, fresh fruits, etc.

Methyl bromide is easily absorbed through the lungs. Thereafter it is quickly distributed to the tissues and rapidly metabolized [4]. Presumably methyl bromide is hydrolysed with the formation of inorganic bromide and methyl alcohol. The cytotoxic effect of methyl bromide is most likely based on its strong alkylating potency. Methyl bromide reacts with amines and sulphur-containing compounds [5]. Its mutagenicity has been established by several researchers [6,7] and it is potentially carcinogenic [8,9].

In methyl bromide poisoning, cytotoxic effects can be expected to occur in virtually any organ system. However, clinical observations suggest a preference for those sites of the body where direct contact can take place (skin, lungs). Dermal exposure can take place either with the liquid or with the gaseous phase of the compound. Following a symptom-free period of several hours, both may lead to erythema and blistering of the skin. Skin lesions are more severe

in areas where perspiration is relatively marked: armpits, groin, genitals. After an acute dermal intoxication an urticarial rash one week after the exposure to methyl bromide may occur. An immunologically mediated mechanism may be hypothesized, possibly with methyl bromide acting as a hapten [10]. Lung damage usually occurs after high-level inhalation exposure. The pulmonary effects are comparable to the adult respiratory distress syndrome and may become manifest after a symptom-free period of several hours. In case of severe exposure, the symptom-free period is of short duration.

Even at lower levels of inhalational exposure, signs of systemic poisoning may develop in the absence of lung damage [11–13]. The central nervous system is the main target organ of methyl bromide. Liver and kidney involvement is also relatively frequent [5]. Symptoms of the central nervous system such as headache, nausea, vomiting, a sense of drunkenness, ataxia, slurred speech, and confusion are the most common and early manifestations of systemic methyl bromide poisoning and may be preceded by a symptom-free interval of several hours [11–13]. Progression to the more severe phase with coma, generalised seizures, myoclonus, and distal axonopathy may follow within hours to days [13,14]. Treatment with diphenylhydantoin, diazepam, paraldehyde, or clonazepam is often not sufficient to suppress convulsive activity. In these cases it may be necessary to resort to anesthesia, with, for example, thiopental. Drug-resistant seizures, also called status myoclonicus, are associated with high mortality [11,14,15]. The myoclonus is usually asymmetrical, distally located, and may occur spontaneously or in response to somato-sensory stimuli. The electroencephalogram may show polyspike and wave complexes with frontal predominance. Also giant somato-sensory evoked potentials may be recorded. Uncini et al. [16] were able to show that the status myoclonicus, as seen in severe intoxications, may represent a form of cortical reflex myoclonus.

Hemoperfusion, chelating agents, and N-acetylcysteine have been used in the management of methyl bromide intoxications, but proved not to be beneficial. Convalescence may take months and not infrequently the patient shows psychiatric disturbances, seizures, action myoclonus and ataxia as residual and sometimes permanent manifestations.

1,3-Dichloropropene (cis- and trans-isomers) and 1,2-dichloropropane

These compounds are volatile soil fumigants which are used as nematocides. They are normally applied by injection under the soil surface, without previous dilution, to control plant parasitic nematodes [17]. They are highly inflammable and air/vapour mixtures can be explosive.

The major route of 1,3-dichloropropene metabolism in the rat is conjugation with glutathione by hepatic glutathione transferase [18,19]. The conjugated product follows the classical mercapturic acid pathway [20] and is excreted in the urine as N-acetyl-S-(3-chloroprop-2-enyl)cysteine and its sulphide [21,22].

The amount excreted has been correlated with time and level of exposure. 1,2 dichloropropane is metabolized in the liver to a variety of metabolic compounds and intermediates [23], for example mercapturic acid metabolites in rats [24]. After exposure to 1,3-dichloropropane the non-protein thiol concentration was significantly reduced [25,26]. Therefore it is suggested that N-acetylcysteine may have a role in the treatment of toxicity from 1,3-di-chloropropane [27,28].

Skin contact can cause severe oedema, redness and necrosis of the skin. After splashing into the eyes severe injury has been observed [29]. Inhalation of the vapour causes mucosal membrane irritation of the nose, throat and airways. Cough, chest pain during breathing and shortness of breath can be observed. In lower concentration a moderate pulmonary involvement may be observed, although central nervous system depression can be considerable, and loss of consciousness may even be the consequence. At higher concentrations (>1500 ppm), inhalation can cause chemical pneumonitis and pulmonary oedema. Ingestion causes pain, diarrhoea and vomiting [30].

After chronic exposure, the primary target organs of 1,3-dichloropropene in experimental animals are the liver and the kidney. In applicators of 1,3 dichloropropane, Brouwer et al. [31] found slight subclinical liver and kidney effects after seasonal exposure from July through October.

Ethylene dibromide

Ethylene dibromide (CH_2BrCH_2Br) is a colourless liquid. The vapour is stable, nonflammable and 3.5 times denser than air. Ethylene dibromide, also known as 1,2 dibromoethane, is used for the fumigation of stored grains, fruits, and vegetables. It is also used for soil disinfection against nematodes. As a fumigant ethylene dibromide is restricted in many countries, because of its carcinogenic potency. It does not appear to be teratogenic.

It can be absorbed through the skin, lungs and gastro-intestinal tract. It appears to be metabolized in vivo by an oxidative pathway (cytochrome P-450) and conjugation pathway (glutathione S-transferase). The metabolites play an important role in its toxicity [32].

Exposure to the higher concentrations in air causes burning of the eyes and upper airways irritation. Following central nervous system stimulation causing a deliriant picture, depression may develop resulting in unconsciousness or coma. Further vomiting can be observed. Hepatic and renal damage may also develop [33].

Splashing of the liquid on the skin causes irritation and a burning sensation. The routine decontamination procedures should be performed. Treatment is symptomatic.

Ethylene dichloride

Ethylene dichloride (CH_2ClCH_2Cl) also called 1,2-dichloroethane, ethylene chloride or sym-dichloroethane, is a colourless liquid. The vapour is not flam-

mable or explosive, and is denser than air. It is also used as a solvent and as a precursor of polyvinyl chloride.

It can be absorbed from the lungs and gastrointestinal tract. Ethylene dichloride is metabolized by enzymes in the microsomal and cytosolic fraction of liver cells [34]. Ethylene dichloride is mainly conjugated with glutathione by means of the GSH-S-transferase [35].

The most commonly observed symptoms are headache, vertigo, abdominal pain, nausea and vomiting. However coma and respiratory arrest have also been observed. In some patients liver and kidney involvement has been observed. Treatment is symptomatic.

Ethylene oxide

Ethylene oxide (CH_2CH_2O) is a colourless gas at ordinary temperatures and 1.5 times denser than air. Because the vapour readily forms an explosive mixture in air, it is usually combined with carbon dioxide to reduce the risk of explosion. Ethylene oxide is now frequently used to sterilize chemically heat-sensitive materials in the hospital setting.

Following inhalation nausea, vomiting, diarrhoea, coughing, headache, general fatigue, dizziness or sleepiness may develop. After severe exposure the patient may develop pareses of the lower extremities, become unconscious, and have seizures. Eye contact with the vapour may result in conjunctivitis. Contact with the liquid may cause severe cornea lesions and necrosis. Splashing the liquid on the skin causes irritation and freezing.

In laboratory animals chronic exposure to ethylene oxide was carcinogenic and mutagenic. Ethylene oxide was mutagenic for human cells. Neurotoxic effects have been described in animals and humans. Recent reports suggest that neuropsychological impairment may be associated with chronic low-level exposure [36,37]. Treatment is symptomatic.

Phosphides

Magnesium phosphide (Mg_3P_2), aluminium phosphide (AlP) and zinc phosphide (Zn_3P_2), are phosphorus preparations which have found a specific place in rodent control. They are pelletized sources of phosphine. Magnesium and aluminium phosphide release phosphine (PH_3) on contact with water. Zinc phosphide releases phosphine in acidic environments. Magnesium and aluminium phosphide are used for fumigation in pest control, and zinc phosphide as a rodenticide. Phosphine is a colourless gas at room temperature and normal atmospheric pressure. It is odourless when pure at a concentration up to 280 mg/m^3 (200 ppm). Phosphine is denser than air. Impurities can cause a garlicky or fish-like odour. Pure phosphine is inflammable at 100°C. Impurities with diphosphine (P_2H_4) in air can be explosive at room temperature.

Phosphine is absorbed following inhalation. No significant absorption can be observed following skin exposure. Phosphine is exhaled and excreted via the

urine after oxidation to phosphite (H_3PO_3) and hypophosphite (H_3PO_2) and phosphate (H_3PO_4). Cumulation of phosphine in the body is unlikely.

After ingestion metal phosphides may be hydrolysed to produce phosphine, which may be absorbed in the gastro-intestinal tract [38–40].

In the poisoned patient abdominal pain, vomiting and restlessness are common initial features, followed by alteration in sensorium, hypotension, and cardiac arrhythmias. Pain and tightness in the chest, pulmonary oedema, dyspnoea, headache, vertigo, tremors, unsteady gait, convulsions and coma may also be observed. In addition liver and renal damage, thrombopenia, and death can ensue within 3–14 days. Chugh et al. [41] suggested involvement of the adrenal gland leading to relatively low plasma cortisol levels. Although phosphine itself is not cumulative in the body, its effects may be cumulative. Deaths have occurred in animals as a result of repeated daily exposures to concentrations below acutely injurious concentrations [42,43]. In man this cumulative effect is not proven [44].

After moving the patient into fresh air, recovery will usually be rapid. At present no biological monitoring method is available. Although it is suggested that steroids may be beneficial for minimizing the chemical pneumonitis and scarring, no adequately evaluated studies are available to support this therapy. Prophylactic antibiotics are generally not indicated and should only be given when a secondary bacterial infection is plausible (fever, leucocytosis, rods in the differential leucocytes cell count, positive bacterial cultures). Treatment is symptomatic.

Metham sodium

Metham sodium (synonyms: methylcarbamodithioic acid sodium salt, methyl-dithiocarbamic sodium salt, sodium methyldithiocarbamate, carbam, vapam, VPM, SMDC [$C_2H_4NNaS_2$]) has an unpleasant odour similar to that of carbon disulphide. It is easily soluble in water and non-flammable. It is used as a soil fumigant to control weeds and weed seeds, nematodes, fungi, and soil insects. In the Netherlands it is the most intensively used soil fumigant. Its activity is due to decomposition to methylisothiocyanate.

It is irritating to the skin and mucous membranes. For further information about dithiocarbamates the reader is referred to the dithiocarbamate section under fungicides. Treatment is symptomatic. Teratogenic effects have been observed in chronic rat studies.

RODENTICIDES

Rodenticides are used to kill rats, mice, moles and other small animals. Most rodenticides are added to baits that are unpalatable to man. Rodenticides can be classified into inorganic compounds including arsenic, thallium, phosphorus, barium carbonate, zinc phosphine, and organic compounds including sodium fluoroacetate, alpha-naphthyl-thiourea, anticoagulants, and strychnine.

Fluoroacetic acid derivatives

Of this group, sodium fluoroacetate ($C_2H_2FNaO_2$) and fluoroacetamide (C_2H_4FNO) are the most commonly used rodenticides. Sodium fluoroacetate is very water soluble and has a low solubility in ethanol, acetone, and other organic solvents.

Sodium fluoroacetate is hardly absorbed through the skin, while fluoroacetamide is absorbed. Fluoroacetic acid derivatives are metabolized into fluorocitric acid. Fluorocitric acid inhibits the cell metabolism at the level of the citric acid cycle [45]. Consequently citrate accumulates in the tissues which may cause hypocalcemia and energy deficiency through blockage of the TCA cycle. Therefore all cells in the body can be involved, especially those cells in the central nervous system. Incubation of ^{13}C-fluoroacetate with rat and mouse liver cytosol involves the formation of S-(carboxymethyl)glutathione and fluoride ion. Fluoroacetate administered intraperitoneally to rats and mice is defluorinated to give fluoride ion in urine and kidney by ^{19}F NMR [46]. Consequently hypocalcemia may also be caused by the fluoride ion. The clinical picture may be caused by accumulation of citrate, by the fluoride ion or by hypocalcemia or the combination of these factors.

Symptoms may develop within minutes to five hours after exposure. Clinical symptoms observed are nausea and vomiting. Central nervous system symptoms which can develop are nystagmus, hallucinations, seizures, and coma. Cardiac arrhythmias, such as ventricular fibrillation, pulmonary oedema and apnoea have also been observed.

Treatment is partly symptomatic. Hypocalcemia should be corrected with, for example, calcium gluconate. In mice a combination of calcium gluconate with sodium succinate has been effective in reducing mortality. Sodium succinate may revive the TCA cycle [47]. Acetamide may be also beneficial, 5 g acetamide should be administered intravenously dissolved in 10% glucose. Depending on the clinical course this should be repeated at intervals of 30 minutes. If acetamide is not available, 5 ml ethanol in 5% glucose administered intravenously may be beneficial.

Anticoagulants

Anticoagulants can be divided into two groups: hydroxycoumarins and indanediones. The hydroxycoumarins include warfarin, warficide, bromadiolone, brodifacoum, diphenadione, coumachlor, coumafuryl, fumasol, and prolin. The indiandiones include valone and pindone, which are the most toxic of the coagulants in use at present. The increased prevalence of rodents resistant to warfarin led to the development of the so called "superwarfarins" for instance the hydroxycoumarin brodifacoum. Brodifacoum has a potency which is about 200-fold that of warfarin. The half-life time is as much as 10–20 times longer than that of warfarin, which is 2–5 days [48,49]. Ingestion of one of the "superwarfarins" may cause marked anticoagulant effects for up to 7 weeks.

Superwarfarins are more lipophilic and have a larger volume of distribution.

All the anticoagulant rodenticides cause a tendency to bleed, due to the inhibition of vitamin K-dependent clotting factors II, VII, IX, and X, and the anticoagulant proteins C and S with consequent prolongation of the prothrombin time. Factors II, VII, IX, and X and protein C and S become biologically inactive unless certain glutamic acid residues are carboxylated by microsomal enzymes which use reduced vitamin K as a cofactor.

Initially no symptoms can be observed in the patient with an overdose. An abnormal prothrombin time (PT) or activated plasma thromboplastin time (PTT) will serve to identify the risk of bleeding complications. Inducing of emesis and gastric lavage are not recommended following ingestion of a regular warfarin compound. Activated charcoal, with a cathartic, may be administered. When ingestion of a long-acting anticoagulant compound is suspected or cannot be ruled out, gastric lavage should be carried out. Also intestinal lavage should be considered. Charcoal and a cathartic should be administered. Further monitoring of the prothrombin time should be checked initially and daily over a period of 2 to 4 days. Prothrombin time values obtained 48 hours after ingestion are more likely to be prolonged than values obtained 24 hours after ingestion [50]. When the prothrombin time is prolonged, vitamin K_1 administration may be necessary for weeks or months [51]. Presumably a dose of 20 mg vitamin K_1 per day is adequate to reverse the coagulopathy; if necessary the dose can be adapted to the prothrombin time. A dose of 100 mg vitamin K_1 per day for a prolonged time caused no complications and was effective in reversing the coagulopathy produced by brodifacoum [52]. The duration of the coagulability is unpredictable, the prothrombin time should therefore be checked 48 hours after stopping vitamin K_1 therapy to detect any recurrence. Vitamin K_3 and K_4 should not be given because these vitamins need to be metabolized into vitamin K_2; therefore reversal of the effects of coumarin derivatives are less effective. When bleeding is manifest, fresh frozen plasma, fresh blood or pooled clotting factors should be given rapidly to stop haemorrhaging.

Strychnine

Strychnine is a very toxic compound with a bitter taste. Elimination kinetics suggest that strychnine follows Michaelis–Menton elimination kinetics. It is a central nervous system stimulant that causes opisthotonos, trismus, risus sardonicus, seizures, and medullary paralysis resulting in death. It results in the competitive antagonism of the inhibitory neurotransmitter at the postsynaptic spinal cord neuron. The patient may remain awake with relaxed muscles between episodes of opisthotonos and seizures.

Treatment includes gastric lavage and activated charcoal, unless symptoms appear; any manipulation or excitement may precipitate the opisthotonos or seizures, and for this reason the patient should be kept in quiet surroundings. The extensor spasms, opisthotonos, and seizures may be controlled by diazepam or phenobarbital. If this proves to be ineffective, general anaesthesia and

muscle relaxation should immediately be considered. Intubation and mechanical ventilation will obviously be required.

Thallium

Thallium sulfate is a colourless, odourless, and tasteless compound that can be absorbed through the unbroken skin. It is rapidly absorbed via the gastro-intestinal tract and by inhalation.

In sublethal doses, thallium can cause nausea, vomiting, and in the first few days after ingestion constipation. Thereafter neuropathic pain is experienced especially in the lower extremities, accompanied with abdominal pain. In the second week after ingestion complete loss of hair, paresthesias and a sensori-motor neuropathy may develop. After about 14 days lunula strips in the nails can be observed.

There is no effective antidote for thallium. Gastric lavage with water followed by multiple doses of Prussian blue and a cathartic is recommended. Prussian blue (ferric ferrocyanide) or Berlin blue (ferric hexacyanoferrate), are both believed to be more effective than activated charcoal in binding thallium and preventing absorption from the gastro-intestinal tract. Prussian blue also prevents intestinal reabsorption.

FUNGICIDES

Fungicides are used to control fungi and bacteria on living and non-living plants and plant parts, as well as on or in all materials and surfaces. Excluded is their use on living humans or animals and all uses on or in processed foods, beverages or pharmaceutical products are prohibited.

Phthalamide fungicides

Captan is a widely used fungicide to protect seeds at planting. It has a low oral toxicity due to rapid degradation in the gastro-intestinal tract. Difolatan belongs to the same group. Captan may cause allergic dermatitis and eye irritation in man [53]. No serious effects have been observed in man.

Copper derivatives

Ammoniacal copper carbonate, cuprous oxide, copper oxychloride, cupric hydroxide, copper sulphate, copper-8-quinolinolate (bioquin I) are sold under a variety of trade names and are usually formulated as wettable powders, water dispersible granules or suspension concentrates. The toxicity is caused by copper.

This group of fungicides is considered to be of a moderate to low hazard and is unlikely to cause poisoning unless deliberately swallowed. In that case, severe symptoms of irritation of the gastro-intestinal tract may be expected.

Internal decontamination of the gastro-intestinal tract may be required. Treatment is otherwise symptomatic.

Dithiocarbamates

The dithiocarbamates are applied on a large scale. Compounds of this group are metam sodium, ferbam, thiram, mancozeb, metiram, propineb, zineb, ziram and maneb. The dithiocarbamates are derivatives of dithiocarbamic acid, with a general molecular structure $(CH_3)_2NC(s)S$-Me, -S-Alkyl, or -S-aryl, where Me is a metal, such as Na^+, Fe^{3+}, Mn^{2+} or Zn^{2+}. Depending on the radical methyl- or ethylene-, and on the metal included in the molecule, different kinds of dithiocarbamates can be obtained, with different properties and uses. Maneb, zineb, ziram, nabam and ferbam are used in agriculture as fungicides. Furthermore maneb and zineb are also used for the storage of wheat seeds, owing to their growth regulation properties.

Dithiocarbamates are considered as fungicides of low toxicity. They inhibit SH-containing enzymes and cause dermatitis, conjunctivitis, rhinitis, pharyngitis and bronchitis in humans. Due to a structural similarity to disulfiram, ethanol consumption after exposure to dithiocarbamate may cause an antabuse-like reaction such as flushing, sweating, headache, weakness, tachycardia and hypotension. Following exposure to a combination product with maneb and zineb in one patient, change in behaviour, tiredness, dizziness and weakness was observed. After a second exposure 6 days later, the same complaints returned. The patient also had a slurred speech, lost consciousness and showed tonic–clonic convulsions. On admission he showed a right hypertonic hemiparesis. After 4 days the patient was discharged without any health effect [54]. Maneb or zineb were not determined and therefore these observations are not conclusive.

Chronic occupational exposure to maneb was associated with the development of a Parkinsonian syndrome in two agricultural workers [55].

Organic mercury compounds

Methylmercury benzoate, ethylmercury bromide, methoxyethylmercury chloride are the most commonly used compounds from this group. Organic mercury compounds are readily absorbed through the skin, gastro-intestinal tract, and lungs. Local irritation may be observed. The toxicity of these compounds is caused by inactivating vital enzymes. Mercury binds to sulfhydryl- (and presumably also to amino-, carboxyl-, and hydroxyl-) groups. Acute toxicity can be observed after exposure to the dust or vapour.

Local irritation of the skin and the mucosal membranes of eyes and airways can develop. Ingestion of these compounds leads to corrosive ulcerations with bleeding and subsequently necrosis of the gastro-intestinal mucosal membranes. Symptoms such as vomiting, hematemesis and bloody diarrhoea can develop. The kidney is very vulnerable to mercuric compounds. Renal failure,

due to necrosis of the proximal tubular epithelium, can occur. Shock ensues from blood and fluid loss by vomiting and diarrhoea, and peripheral vascular dilatation by the relaxation of smooth vascular muscles due to metabolic acidosis. Further neurological symptoms like headache, tremor, neuralgia, ataxia, mental disturbancies and coma may develop.

In chronic intoxication the neurological symptoms are more prominent. They start with tiredness, lack of concentration, short memory, and headache. A more severe intoxication causes peripheral and central nervous system damage causing tremor, cerebellar ataxia, cortical atrophia, dysarthria, deafness, anaesthesia, paraesthesia, hallucinations, delirium and concentric loss of visual field.

Methylmercury readily crosses the placenta. Exposure during pregnancy can produce cerebral palsy in infants even when signs of poisoning are mild in the mother during pregnancy. These effects can be explained by an inhibitory action on two key processes in brain development, namely neuronal migration and cell division. Inhibitory action on these two processes has been demonstrated by experimental work [56]. In less severe cases, prenatal exposure produces delayed achievement of developmental milestones and more subtle neurological disturbances.

Treatment consists of prompt decontamination of the gastro-intestinal tract, to reduce further absorption and to limit the corrosive action on mucosal membranes. Therefore medical suppression of vomiting may be useful to protect the eosophagus mucosae. Immediate administration of an appropriate chelating agent has to be instituted to increase excretion. Until recently dimercaprol (BAL) was the preferred chelating agent since it can mobilize mercury from the kidneys and may protect against kidney damage [57]. However, the complexes formed by BAL appear to accelerate the redistribution of mercury to tissues with resulting increase in brain mercury levels. In addition BAL can accumulate to toxic levels in anuric patients. Therefore BAL has therapeutic limitations, especially in anuric patients. More recently 2,3-dimercapto-1-propanesulfonic acid (DMPS), a water-soluble derivative of dimercaprol with lower local and systemic toxicity, is marketed for both parenteral and oral administration. In experimental studies DMPS very effectively reduced mercury content in the kidneys and increased urinary, as well as biliary mercury excretion [58–62]. Because DMPS may also increase the urinary excretion of trace elements (copper, zinc) special attention should be paid to prevent depletion in these elements [63]. The initial dose of DMPS is 250 mg dissolved in saline. Thereafter every 4 hours for the first 48 hours, 250 mg every 6 hours in the second 48 hours, and 250 mg every 8 hours afterwards. Treatment should be continued until mercuric blood and urine concentration is decreased below 100 μg/l [63]. Hemodialysis or hemoperfusion proved to be of little or no value in enhancing mercury elimination [63–65].

Organic tin compounds

The trisubstituted organotin compounds (tributyltin chloride, linoleate, oxide, triphenyltin chloride, acetate, hydroxide, tricyclohexyltin hydroxide) have biocidal properties. The most important compounds are the tributyl-, triphenyl- and tricyclohexyltin compounds. They are used as agricultural and general fungicides, bactericides, antihelminthics, miticides, herbicides, molluscicides, insecticides, rodent repellents, and antifoulants in boat paints. The main route of entry is the respiratory tract. During the processing of tin or tin compounds considerable exposure may occur. A certain degree of cutaneous absorption, however, cannot be excluded. The trialkyltin compounds are usually easily absorbed through the skin. In general, the absorption of ingested organotin occurs more readily than that of inorganic tin compounds. As a rule, tin compounds with a short alkyl chain are more readily absorbed from the intestinal tract.

Many organic compounds are transformed, to some extent, in the tissues. Dealkylation and dearylation of tetra-, tri-, and di-substituted organotin compounds seem to occur in the liver. Excretion via the urine, bile and faeces depends on the type of organic tin compound. Usually the biological half-life seems to be longer in the brain than in other organs. In general, mono- and di-organic tin compounds are less toxic than triorganic compounds. The toxicity of trialkyltin compounds decreases as the number of carbon atoms in the alkyl chain increases.

Dibutyl- and tributyltin compounds produce skin irritation in workers 1–8 hours after contact. Skin lesions were most commonly caused by small splashes of liquid dibutyl or tributyl tin chlorides. If the compounds are removed immediately, no lesions will develop. These compounds also produced eye irritation after contact [66–68]. Exposure of the upper respiratory tract and eyes of spray-painters to tributyltin vapours of latex paint caused mucosal irritation. Bloody discharge was also observed from the nose [69]. The most common clinical picture was characterized by impairment of the central nervous system with interstitial oedema of the white matter. The mechanism of trimethyltin-induced neuronal necrosis is unknown, as is the reason for the preferential localization in the hippocampus and the pyriform cortex [70]. Clinical symptoms include headache, dizziness, photophobia, visual disturbances, blindness, nausea, vomiting, and abdominal pain. Sometimes there is temporary loss of consciousness and seizures. An increase of liver enzymes activities and kidney function impairment have also been described in rats and mice [71,72]. Short-term (4-week) exposure of rats to tributyltin oxide induced atrophy of the thymus and peripheral lymphoid organs [73]. Tributyltin oxide suppresses thymus-dependent immune responses as well as parameters of the nonspecific resistance [74] in rats after 6,9-week exposure. Chronic exposure to tin oxide may result in benign pneumoconiosis.

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23. Volatile substances with special reference to volatile substance abuse

INTRODUCTION

Exposure to the vapour of organic solvents and other volatile compounds may occur during the manufacture and use of many products (Table 23.1) and has been associated with toxicity in some instances (Table 23.2). However, if anesthesia is excluded, acute poisoning with volatile substances nowadays usually arises from the deliberate inhalation of vapour in order to become intoxicated, so-called "glue sniffing", inhalant abuse, solvent abuse, volatile solvent abuse, or volatile substance abuse (VSA).

Those who ingest, or more rarely inject, solvents or solvent-containing products, either accidentally or deliberately, and the victims of industrial, clinical and domestic accidents, may also be poisoned by these compounds. In addition, chloroform and other volatiles are still used occasionally in the course of crimes such as rape and murder [10].

Deliberate inhalation of amyl (isopentyl) and isobutyl nitrites may also be encountered. The hazards associated with the abuse of these compounds have been reviewed [11]. The pharmacological effect (vasodilation) of these compounds is markedly different from those of volatile substances *per se* and thus nitrites will not be discussed further here except in so far as they may be encountered in samples sent for toxicological analysis. Similarly, poisoning with overtly toxic volatile substances such as chlorine is not considered here, even though such compounds are sometimes inhaled deliberately [12].

Nomenclature of volatile compounds

One problem encountered when discussing volatile substances is the multiplicity of chemical and trivial names in common use. Systematic names, common synonyms/abbreviations and Chemical Abstracts Service (CAS) Registry numbers for many volatile substances are given by Streete et al. [13] and by de Zeeuw et al. [14]. In this chapter, straight-chain (normal) alkanes are

Manufacture of/use as	Areas of use
Adhesives	Agriculture
Aerosol propellants	Art studios
Anesthetics	Chemical industry
Chemical warfare agents	Degreasing
Detergents	Dry cleaning
Drugs	Fat processing
Explosives	Food processing
Fire extinguishers	Laboratory work
Fuels	Leather japanning
Inks	Medicine/Dentistry
Laboratory chemicals	Photography
Lubricants	Painting/Paint stripping
Paints, enamels and lacquers	Printing
Paint thinners	Wood preservation
Perfumes	Pesticides
Pesticides	
Refrigerants	
Resins	
Rubber	
Sealants	
Stains, dyes and varnishes	
Waxes	

Table 23.1. *Some uses of volatile substances*

Compound	Hazard	References
Acetonitrile	Cyanide produced *in vivo*	Amdur [1]
Benzene	Blood dyscrasias	Yardley-Jones et al. [2]
Bromomethane	Peripheral neuropathy, ataxia, behavioural changes	Anger et al. [3]
Carbon disulphide	Fatigue, sleep disturbances, peripheral neuropathy, muscle weakness	Davidson and Feinleib [4]
Carbon tetrachloride	Hepatorenal toxicity	Proctor et al. [5]
Dichloromethane	Carbon monoxide *in vivo*	Stewart and Hake [6]
1,2-Dichloropropane	Hepatorenal toxicity	Pozzi et al. [7]
Hexane	Peripheral neuropathy	Lancet [8]
2-Hexanone (methyl butyl ketone, MBK)	Peripheral neuropathy	Lancet [8]
Methanol	Optic neuropathy	Proctor et al. [5]
Nitrous oxide	Myeloneuropathy	Layzer [9]
1,1,2,2-Tetrachloroethane	Hepatorenal toxicity	Proctor et al. [5]

Table 23.2. *Hazards reported from occupational exposure to common volatile substances*

referred to by name with no suffix (hexane, for example). In some cases widely-used trivial names (chloroform, carbon tetrachloride) have been preferred to systematic names. In the case of mixed ethers and ketones the convention has been adopted whereby the substituent with the lowest carbon number is cited first, for example methyl tert.-butyl ether. Compounds used as drugs are referred to by their approved names.

With halons (halocarbons, aliphatic hydrocarbons in which one or more hydrogens are replaced by halogen atoms) there are two separate "shorthand" numbering systems. The simplest system was promulgated by the United States (US) Army Corps of Engineers in the late 1950s and uses the word "halon" together with a number denoting (reading from left to right) the numbers of carbon, fluorine, chlorine and bromine atoms in the molecule; terminal zeros are omitted. The number of hydrogens is calculated by difference. Clearly for anything but very simple molecules this notation gives a group" classification.

The second halon numbering system was devised by the American Society of Refrigeration Engineers (ASRE) for substituted methane, ethane and cycloalkane refrigerants, and has since been extended to include other fluoroaliphatics. In this system all fluorocarbons (FCs) have an identifying number, the first digit (reading from right to left) being the number of fluorine atoms in the molecule, the second from the right being the number of hydrogens plus 1, and the third from the right being the number of carbons minus 1 (omitted if zero). The number of chlorines is ascertained by difference. In unsaturated compounds the number of double bonds is shown by the fourth number from the right; bromine is indicated by a capital "B" followed (on the right) by a number indicating the number of bromine atoms present; different isomers are indicated by lower case suffixes ("a", "b", etc.) allocated in order of decreasing symmetry, and so on.

Clearly, the ASRE fluorocarbon numbering system is unwieldy with complex molecules. Moreover, the numbers derived in this manner are sometimes used together with the words "propellant" or "refrigerant", or with a variety of trade (brand) names including Arcton (ICI), Freon (Du Pont), Frigen (Hoechst), Genetron (Allied-Signal), Isceon (Rhône-Poulenc), Isotron (Pennsalt), KLEA (ICI) and Ucon (Union Carbide). These trade names may also be used with numbers not derived using the ASRE system to denote azeotropic FC mixtures. In addition, numbers based on the ASRE fluorocarbon system are sometimes used with the suffixes "C" and/or "H" to denote the presence of chlorine or hydrogen, respectively, in the molecule.

VOLATILE SUBSTANCE ABUSE

Compounds such as chloroform, diethyl ether and nitrous oxide have been deliberately inhaled for recreational purposes since the early 1800s. Diethyl ether and chloroform especially were widely abused in the latter part of the nineteenth century [15,16]. Deliberate inhalation of substances such as trichloroethylene in Germany [17], and of products such as petrol (gasoline) in the US

[18], was recorded as they became widely available. VSA has now been reported from most parts of the world, mainly amongst adolescents, individuals living in remote communities, and those whose occupations give ready access to abusable substances. Many reviews, monographs, proceedings of meetings, and consultation documents on VSA have been published in the last few years [19–25].

Products which can be abused by inhalation must contain a suitably volatile substance which is accessible in sufficient quantity free from overtly toxic components. Solvents from contact adhesives, notably toluene, typewriter correcting fluids and thinners (until recently commonly 1,1,1-trichloroethane), other halogenated solvents, hydrocarbons such as those found in cigarette lighter refills [liquified petroleum gas (LPG), largely butane], aerosol propellants, halocarbon fire extinguishers, and inhalational anaesthetics such as enflurane and nitrous oxide are amongst the compounds/products which may be abused in this way (Tables 23.3 and 23.4). Petrol (gasoline) is still often abused, especially in less developed communities [19,26–29]. Note however that petroleum distillates such as white spirit and paraffin (kerosene), and also alcohols and diols such as ethanol, 2-propanol, 2-methoxyethanol (methyl cellosolve) and ethylene glycol, are not sufficiently volatile to be abused by inhalation.

Many of the substances which can be abused by inhalation remain in widespread use. However, since the 1970s concern about the consequences to the environment of the release of massive quantities of volatile organochlorine and organobromine compounds such as chlorofluorocarbon (CFC) refrigerants and aerosol propellants into the atmosphere has led to the planned phased withdrawal of many CFCs, chlorinated solvents, and halocarbon fire extinguishers (Montreal Protocol, Figure 23.1). Deodorised LPG and dimethyl ether (DME), which is often used as a non-flammable azeotrope with chlorodifluoromethane, have already largely replaced fully halogenated CFCs as aerosol propellants in many countries.

It remains to be seen which volatile halogenated compounds will be in widespread use by the year 2000. Polyfluorinated compounds such as 1,1,1,2-tetrafluoroethane are being produced for use as refrigerants. Dichloromethane, tetrachloroethylene and trichloroethylene look set to replace 1,1,1-trichloroethane in many applications. Such changes are unlikely to have a major impact on VSA since the replacement compounds have just the same potential for abuse as CFCs. However, if halocarbon fire extinguishers are replaced by extinguishers containing carbon dioxide and if 1,1,1-trichloroethane-based correction fluids are replaced by water- or oil-based products then two sources of abusable volatiles will have been removed.

VSA clearly has much in common with other forms of substance abuse on the one hand and with ethanol (alcohol) use on the other. Solvents and other abusable volatiles can produce dose-related central nervous system (CNS) effects similar to those of other sedative and hypnotic agents. Small doses can rapidly lead to euphoria and other behavioural disturbances which are similar

1. Hydrocarbons:		
	Aliphatic	Acetylene
		Butane[1]
		Isobutane (2-methylpropane)[1]
		Hexane[2]
		Propane[1]
	Alicyclic/aromatic	Cyclopropane (trimethylene)
		Toluene (toluol, methylbenzene, phenylmethane)
		Xylene (xylol, dimethylbenzene)[3]
	Mixed	Petrol (gasoline)[4]
	Halogenated	Petroleum ethers[5]
		Bromochlorodifluoromethane (BCF, FC 12B1)
		Carbon tetrachloride (tetrachloromethane)
		Chlorodifluoromethane (FC 22, Freon 22)
		Chloroform (trichloromethane)
		Dichlorodifluoromethane (FC12, Freon 12)
		Dichloromethane (methylene chloride)
		1,2-Dichloropropane (propylene dichloride)
		Ethyl chloride (monochloroethane)
		Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane)
		Tetrachloroethylene (perchloroethylene)
		1,1,1-Trichloroethane (methylchloroform, Genklene)
		1,1,2-Trichlorotrifluoroethane (FC 113)
		Trichloroethylene ("trike", Trilene)
		Trichlorofluoromethane (FC 11, Freon 11)
2. Oxygenated compounds		Acetone (dimethyl ketone, propanone)
		Butanone (2-butanone, methyl ethyl ketone, MEK)
		Butyl nitrite[6]
		Enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether)
		Ethyl acetate
		Diethyl ether (ethoxyethane)
		Dimethyl ether (DME, methoxymethane)
		Isobutyl nitrite ("butyl nitrite")[6]
		Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether)
		Isopentyl nitrite (isoamyl nitrite, amyl nitrite)[6,7]
		Methyl acetate
		Methyl isobutyl ketone (MIBK, isopropyl acetone)
		Methyl tert.-butyl ether (MTBE)
		Nitrous oxide (dinitrogen monoxide, "laughing gas")
		Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether)

1 Principal components of Liquified Petroleum Gas (LPG).
2 Commercial "hexane" is a mixture of hexane and heptane with small amounts of higher aliphatic hydrocarbons.
3 Mainly meta-xylene (1,3-dimethylbenzene).
4 Mixture of aliphatic and aromatic hydrocarbons with boiling range 40–200°C.
5 Mixtures of pentanes, hexanes, etc. with specified boiling ranges (for example 40–60°C).
6 Abused primarily for its vasodilator properties.
7 Commercial "amyl nitrite" is mainly isopentyl nitrite but other nitrites are also present.

Table 23.3. *Some volatile substances which may be abused by inhalation*

Product	Major volatile components
Adhesives:	
Balsa wood cement	Ethyl acetate
Contact adhesives	Butanone, hexane, toluene and esters
Cycle tyre repair cement	Toluene and xylenes
Polyvinylchloride (PVC) cement	Acetone, butanone, cyclohexanone, trichloroethylene
Woodworking adhesives	Xylenes
Aerosols:	
Air freshener	LPG, DME and/or fluorocarbons
Deodorants, antiperspirants	LPG, DME and/or fluorocarbons
Fly spray	LPG, DME and/or fluorocarbons
Hair lacquer	LPG, DME and/or fluorocarbons
Paint sprayers	LPG, DME and/or fluorocarbons and esters
Anaesthetics/analgesics:	
Inhalational	Nitrous oxide, cyclopropane diethylether, halothane, enflurane, isoflurane
Topical	FC 11, FC 12, monochloroethane
Dust removers ("air brushes")	DME, FC 22
Commercial dry cleaning and degreasing agents	Dichloromethane, FC 113, methanol, 1,1,1-trichloroethane, tetrachloroethylene, toluene, trichloroethylene (now rarely carbon tetrachloride, 1,2-dichloropropane
Domestic spot removers and dry cleaners	Dichloromethane, 1,1,1-trichloroethane, tetrachloroethylene, trichloroethylene
Fire extinguishers	Bromochlorodifluoromethane, FC 11, FC 12
Fuel gases:	
Cigarette lighter refills	LPG
"Butane"	Butanes and propane
"Propane"	Propane and butanes
Nail varnish/nail varnish remover	Acetone and esters
Paints/paint thinners	Acetone, butanone, esters, hexane, toluene, trichloroethylene, xylenes
Paint stripper	Dichloromethane, methanol, toluene
Room-odorizer"	Isobutyl nitrite
Surgical plaster/chewing gum remover	1,1,1-Trichloroethane, trichloroethylene
Typewriter correction fluids/thinners	1,1,1-Trichloroethane
Whipped cream dispensers	Nitrous oxide

See Table 23.3 for full chemical names of some compounds. Halocarbon shorthand nomenclature is summarized on page 579.

***Table 23.4**. Some products which may be abused by inhalation*

The Montreal Protocol is an international agreement on the manufacture and import/export of the volatile chlorinated and brominated compounds listed below. Originally it was planned to gradually reduce the use of these controlled substances to zero by the year 2000 (2005 in the case of 1,1,1-trichloroethane) with a 10-year extension granted for less developed countries. Manufacture of some controlled substances was still to be permitted for safety-critical and other "essential" applications such as use in medical inhalers, as fire extinguishers, or for captive use as chemical intermediates. Not all countries have signed the agreement. A revised timetable (see below) was adopted in Copenhagen in November 1992. Cutbacks are from 1986 production. The European Community has advocated tighter controls, including the phase-out of chlorofluorocarbons containing at least 1 hydrogen atom (HCFCs) by 2014.

Controlled Substances (N.B. Details of fluorocarbon nomenclature are given on page 579.

a. Chlorofluorocarbons (denoted CFCs in the protocol) — FCs 11, 12, 113, 114, 115 and all other fully halogenated chlorofluorocarbons with 1, 2 or 3 carbon atoms, including all isomers: 75% cut in production by 1.1.1994; complete phase-out by 1.1.1996.

b. Bromofluorocarbons (denoted halons in the protocol) — FCs 12B1, 13B1 and 114B2, including all isomers: complete phase-out by 1.1.1994.

c. Carbon tetrachloride: 85% cut in production by 1.1.1995; complete phase-out by 1.1.1996.

d. 1,1,1-Trichloroethane: 50% cut in production by 1.1.1994; complete phase-out on 1.1.1996.

e. Chlorofluorocarbons with 1, 2 or 3 carbon atoms containing at least one hydrogen atom (HCFCs, e.g. FC 21, FC 22, etc.): no increase in production from 1996; complete phase out by 2030.

f. Bromomethane: cut in production (to 1991 levels) by 1995; further cuts likely in future.

Fig. 23.1. *Montreal Protocol 1987.*

to those caused by ethanol, and may also induce more profound effects such as delusions and hallucinations. Psychological dependence is common in chronic users, although withdrawal symptoms are rarely severe [30]. Higher doses may produce life-threatening effects such as convulsions and coma. Death may ensue indirectly after, for example, inhalation of vomit, or from direct cardiac or CNS toxicity [31].

Deep breathing through the nose and mouth is often involved when volatile substances are abused". Re-breathing exhaled air may add to the effect if the solvent vapour is contained in a plastic or paper bag [32]. It is virtually impossible to assess dosage. It seems likely that the intensity of abuse (and consequent exclusion of oxygen) is a risk factor in sudden deaths. Chronic toxicity from VSA is uncommon and is related not only to the intensity and

duration of abuse, but also to the compound(s) abused. Chronic high-dose usage of toluene-containing products and of chlorinated solvents such as 1,1,1-trichloroethane, for example, can produce severe organ damage, especially in the liver, kidneys, and brain.

Modes of abuse of volatile substances

The physical form of a product often determines the mode of abuse. Contact adhesives are usually poured into plastic bags such as empty potato crisp packets or paper bags. The top is then gathered together and placed over the mouth and the vapour inhaled ("bagging"). It is sometimes reported that cans of glue are heated to increase the yield of vapour. Some abusers may use 4-6 litres of adhesive weekly [33,34]. Petrol and other relatively volatile solvents may be inhaled directly from the container, or first poured onto fabric, for example a coat sleeve or a handkerchief ("huffing"), or into cut down plastic bottles, such as empty detergent or bleach containers. There are clear risks of fire and explosion associated with petrol sniffing" [35] and also with the abuse of LPG cigarette lighter refills [36].

Aerosols are usually liquid or solid suspensions supplied in cans containing a liquified propellant gas. These products and also halon-containing fire extinguishers may be inhaled after spraying into plastic bags or under bedclothes. At room temperature one volume of liquid propellant may generate 200 to 300 volumes of vapour. The normal use of the product is largely immaterial to the abuser, although products containing a high proportion of propellant, such as topical analgesic (pain relief) sprays (100% propellant), deodorants, and fly sprays are preferred to those with little (shaving foam, for example). If some constituents are not respirable, for example aluminium chlorhydrate (a toxic active ingredient in antiperspirants), then the product may be first bubbled through water, filtered through a cloth held firmly over the mouth, or sprayed into a plastic bag and the aerosol allowed to settle. Deaths have occurred from drowning as a result of abuse of aerosols in the bath, the bath water possibly having been used to "scrub" out the unwanted components of the aerosol. Alternatively, the aerosol container may be inverted allowing direct access to the propellant via the dip tube. Abuse of nitrous oxide from cylinders designed for use, for example, with whipped cream dispensers has also been described [37]. Deliberate misuse of salbutamol- and beclomethasone-containing aerosols has been attributed to abuse of the propellant [38–40], even by a 4-year-old [41]. Finally, abuse of propellants used to power spray painting equipment is commonly-reported in the US and Japan, but is not common in the United Kingdom.

Domestic fuel ("natural") gas is rarely abused, primarily because the principal component, methane, does not induce the desired pharmacological effects. However, the gas used in cigarette lighter refills, small blow torches and camping gas stoves (butane with smaller amounts of isobutane, propane and unsaturated components) is commonly abused. These products are available in small, inexpensive packs (250 ml or so). Use of 5–10 cans/day has been

described [42]. Gas from larger containers (sometimes propane) is also abused [43,44]. These latter containers are filled to relatively high pressures and usually need a valve with which to obtain the gas. However, the contents of LPG cigarette lighter refills may be inhaled by holding the can upright, clenching the nozzle between the teeth and pressing to release the gas. If such cans are tilted a jet of fluid cooled to at least –40°C by expansion may be released which may cause burns to the mouth [45], and possibly even to the throat and lungs. Consequent mucosal oedema may cause respiratory difficulties, while rapid chilling of the larynx may result in death from vagal stimulation.

Prevalence of volatile substance abuse

There has been no systematic survey of the incidence of VSA in the UK. In 1984 to 1986, a mean prevalence of previous or current VSA of 5.9% was reported in adolescent school children in London [46]. The proportion of abusers ranged from 0.5 to 9.6% over the 16 schools surveyed with no marked sex difference. However, if subjects who had never been "intoxicated" were excluded, the mean prevalence fell to 3.6%. In a survey in South Wales in 1985, of 4766 pupils aged 11 to 19 years, 6.1% had tried VSA and a further 0.7% were current abusers; three pupils (0.1%) "sniffed" every day [47]. Of those who had experimented with VSA, 58% had sniffed by the age of 13 years. Three further studies have reported higher prevalence rates (8% of 14 to 16-year-olds in the most recent study), although the criteria used to select the schools surveyed are unclear [48–50]. Several other surveys performed in the community within the last few years have given similar results.

Thus, it seems that overall some 3.5 to 10% of young people (equal numbers of males and females) in the UK have at least experimented with VSA and that some 0.5 to 1% of the secondary school population are current users. O'Bryan [51] commented that in the UK the problem seems virtually confined to Caucasians, but cautioned against over-reliance on the results of surveys taken at one time in one area since VSA is well-known to be sporadic in nature. Indeed, surveys in particular groups within the last 10 years have shown a much higher incidence of VSA. These surveys included problem drug users in Bristol aged 10–44 years [17% incidence of VSA [52]], consecutive admissions to a drug abuse treatment in London [43% incidence of VSA [53]], delinquents in an institutional school in Scotland [80% had tried VSA [54]], and inmates in a Secure Unit in Belfast [66% VSA [55]]. Of course some of these figures are very high because VSA was probably a factor in selection for the group in the first place. On the other hand, secondary school-based studies in adolescents may underestimate the incidence of VSA in this age group since chronic abusers may well have left school before non-abusers.

Similar, if not slightly higher, figures for the prevalence of VSA have been reported from other countries within the last 10 years. Some 10% of young people aged 15 to 20 years in Oslo, Norway, had "sniffed" at some stage [56]. In three secondary schools in Yugoslavia (2,254 pupils, aged 14–18 years), 15.2%

of the boys and 11% of the girls were "sniffers" [57]. In the US, lifetime prevalence of VSA as recorded in the National High School Senior Drug Abuse Survey increased from 12.5% in 1979 to 17% in 1989 [58]. More recently, abuse of volatiles (excluding nitrites) amongst 31,782 high school seniors in the US was recorded as: ever used (%), 11.2; used in past year, 4.3; used in past month, 1.6 [59]. Of 1836 students aged 9 to 18 years from a deprived socio-economic background in Sao Paolo, Brazil, some 24% had abused volatile substances at some stage, 4.9% within the previous month [60]. The substances most commonly abused were "lança-perfume" (a mixture of chloroform and diethyl ether) (36%), acetone (34%), petrol (32%), finger-nail polish (31%) and glue (25%).

Thus, VSA is an important, perhaps increasing, problem amongst adolescents in many developed and less developed countries [25]. Several factors contribute to the continuing popularity of VSA in this age group. The products abused are cheap and readily available. Furthermore, the containers, for example those of typewriter correction fluid and thinner, are conveniently sized and are either easily concealed or their possession can appear legitimate. Unlike under-age purchase of alcoholic drinks, VSA is not illegal in the UK and in many other countries. Moreover, the onset of effects and recovery can be rapid, a distinct advantage over alcohol because a child who "sniffs" after school can still return home sober. This is especially true of the abuse of LPG and other very volatile substances. VSA is often a group activity and peer-group pressure may be a factor in encouraging the persistence of the practice. It has been suggested that toluene users are more likely to "sniff" in a group setting, possibly because of the relatively long duration of intoxication with this compound [61]. However, Jacobs and Ghodse [53], for example, reported that most of their group of abusers used butane in a group setting.

Whilst adolescent volatile substance abusers are clearly a major cause for concern, a further numerically smaller group is no less worrying. This comprises those who abuse volatile substances encountered in the workplace. Dentists and anaesthetists are prime examples — it has been estimated that some 1 to 1.6% of dentists in the US were abusing nitrous oxide in 1979 for example [62]. Between 1984 and 1987 there were at least 11 workplace fatalities in employees in the US from abuse of nitrous oxide intended either to power whipped cream dispensers (n = 6) or for dental/hospital use [37]. During 1961-1980, out of 384 cases of workplace poisoning by inhalation of tetrachloroethylene, 1,1,1-trichloroethane or trichloroethylene, there was evidence of deliberate abuse in 9 cases [63]. A similar analysis of cases of workplace poisoning due to dichloromethane, toluene, styrene or xylene also noted cases of deliberate exposure [64]. These latter studies will of course not record incidents such as deaths occurring outside the workplace even though the habit may have been acquired at work. Some of the problems of assessing VSA in the workplace have been discussed [65]. Whilst the risks of VSA to the abusers themselves are obvious, the risks to other employees and to patients and others who might be affected by the actions of an intoxicated employee are no less worrying.

Volatile substance abuse — Clinical presentation

VSA is characterised by a very rapid onset of intoxication and a relatively rapid recovery; a "high" can be maintained for several hours by repeated "sniffing". As with the ingestion of alcohol (ethanol), euphoria, disinhibition and a feeling of invulnerability may occur. Higher doses often lead to less pleasant and more dangerous effects. Changes in perception may precede bizarre and frightening hallucinations while blurred vision, tinnitus, dysarthria, ataxia, agitation, limb and trunk incoordination, tremors, unsteady gait, hyperreflexia, confusion, muscle weakness, headache, abdominal cramps, chest pain, irritability, belligerence, impaired judgement and dizziness are often reported; dangerous delusions such as those of being able to fly or swim may also occur [66]. Nausea and vomiting with the risk of aspiration can occur at any stage. Flushing, coughing, sneezing and increased salivation are further characteristic features. Stupor, coma, depressed respiration and even convulsions may ensue in severe cases [67]. Hemiparesis, possibly due to cerebral artery spasm, has also been reported after butane inhalation [68].

The following case reports illustrate aspects of the acute presentation of volatile substance abusers.

Non-chlorinated hydrocarbons. A 24-year-old man who had "sniffed" paint fumes (petroleum ether and toluene) was admitted to hospital with a 3-day history of muscle weakness. On examination he was found to have profound muscle weakness, being unable to hold a pen or to walk, acute respiratory failure and a metabolic acidosis. He suffered a respiratory arrest approximately three hours after admission, but was resuscitated and required mechanical ventilation for three days before recovery [69].

A 21-year-old male normally used four litres per week of a contact adhesive containing toluene. After a six-hour "sniffing" session he suffered respiratory arrest before and again after admission to hospital. Cardiac arrhythmias were absent on both occasions and there was no report of muscle weakness. The urinary hippuric acid concentration was 2.5 g/l (normally 0.1 to 0.2 g/l). The toxicology screen was otherwise negative [33].

A 16-year-old boy used four to six litres of toluene-containing contact adhesive weekly. He was found collapsed in a swimming pool after "sniffing". He recovered spontaneously but collapsed again after five minutes. The cardiac monitor of the local mobile coronary care unit showed ventricular fibrillation which required nine direct current shocks before he reverted to sinus rhythm. An electrocardiogram showed acute anterior myocardial infarction [34]. Profound sinus bradycardia on admission after toluene inhalation with muscle weakness, gastrointestinal complaints, and rhabdomyolysis has also been reported [70].

Ventricular tachycardia [71], ventricular fibrillation [72] and asystole [73] after inhalation of butane have also been described. Electrophysiological studies in a 14-year-old girl who suffered ventricular fibrillation after "sniffing" lighter fuel demonstrated an atrio-ventricular junctional re-entry tachycardia; it was suggested that preexisting cardiac disease could possibly be a factor in

increasing the risk of arrhythmias after VSA [74].

A 38-year-old man with a six-month history of glue sniffing developed liver cell injury (AST 6855 U/l, ALT 10,425 U/l), myonecrosis (CPK 341 U/l) and acute oliguric renal failure (thought probably to be acute toxic tubular necrosis) following repeated glue sniffing for eight hours [75]. The presumptive agent was toluene though this was not confirmed analytically. The patient made a full recovery.

Fatal fulminant hepatic failure in a 17-year-old abuser of butane-containing aerosols (5–10 cans per day for 3 years) two days after ingesting a proprietary engine/carburettor cleaner has also been reported [42]. The cleaning agent contained a mixture of 2-propanol, 2-methyl-1-pentanol, butylated hydroxytoluene and a range of petroleum products. The authors suggested that microsomal enzyme induction attributable to heavy butane abuse may have played a part in the development of hepatic failure.

Chlorinated hydrocarbons. Wodka and Jeong [76] described a 15-year-old boy who was found in cardiorespiratory arrest after abusing typewriter correction fluid containing trichloroethylene and 1,1,1-trichloroethane. Defibrillation was performed and sinus rhythm established. Subsequent examination revealed acute anteroseptal myocardial injury; coronary artery spasm may have been the mechanism of myocardial injury. The ability of trichloroethylene to produce cardiac arrhythmias is well known from its use as an anaesthetic. Halogenated anaesthetics such as halothane, and possibly also non-halogentated hydrocarbons such as toluene, may have synergistic toxic effects in patients exposed to chlorinated solvents either occupationally or as a result of VSA [77,78].

Sudden volatile substance abuse-related death

The major risk associated with VSA is that of sudden death. Bass [79] reported 110 such deaths in the US from abuse of aerosol propellants and chlorinated solvents during the 1960s. There were at least 114 VSA-related deaths in the US in 1974 [80]. Further series of fatalities have been noted, again from the US [81,82], from Scandinavia [83,84], and more recently from Japan [85] and from Australia [19]. In the UK, sudden deaths from VSA have been monitored systematically since 1983 [86,87] and have increased from 2 in 1971 to 122 in 1991, the latest year for which figures are available. The highest number of deaths recorded in any one year was 151 in 1990. Deaths arising from the consequences of chronic VSA such as renal failure were excluded. Instances where poisoning with a volatile compound was the direct cause of sudden death, but where there was no evidence of VSA, were also excluded. However, some suicides where there was evidence of mental disorder induced by VSA were included (Ramsey, personal communication).

The UK National Poisons Information Service recorded a large increase in requests for information about VSA in the late 1970s and early 1980s [88]. From 1983 to 1991 the average annual increase in VSA-related sudden deaths

was 5.4% per year (annual numbers of deaths rose steeply at first but the rate of increase has diminished in recent years). VSA-related deaths remain relatively rare in the UK given the numbers of abusers indicated by prevalence studies. VSA-related deaths occur in all social classes in the UK and in all parts of the country. In few cases is transport to hospital even attempted. The age at death has ranged from 9 to 76 years, but most deaths (73%) occur in adolescents aged less than 20 years. In contrast to the sex distribution noted in prevalence studies, most VSA-related deaths in the UK (88%) have occurred in males. In 1991, in 46 (38%) of 122 UK VSA-related deaths either there was evidence suggesting that death occurred on the first occasion (or on one of the first occasions) of abuse, or there was no evidence of the deceased ever having indulged in VSA before [87].

The compounds encountered in UK VSA-related sudden deaths (1971–1991) are: fuel gases, mainly LPG from cigarette lighter refills (35% of cases); aerosol propellants, i.e. fluorocarbons and/or LPG (21%); solvents from adhesives (19%); other solvents, notably 1,1,1-trichloroethane (21%); and fire extinguishers (mainly bromochlorodifluoromethane) (4%). Inhalation of alkyl nitrites was responsible for 5 deaths, all in males aged more than 30 years (Ramsey, personal communication). Deaths due to solvents in glues have decreased somewhat following the introduction of legislation aimed at preventing sales to abusers. Since 1989, deaths due to fuel gases have shown a slight proportionate decrease [87], but nevertheless remain associated with a high proportion of deaths (38% in 1991).

There are no published data on VSA-related deaths from other countries comparable to those available in the UK, although individual cases and small series of deaths are reported regularly. VSA-related deaths are now so common, however [at least 1,237 in the UK alone, 1971 to 1991 [87]], that the continued publication of case reports contributes little to our knowledge of VSA except in instances where some feature of the case or its investigation is especially noteworthy. VSA-related mortality statistics, on the other hand, do provide a crude measure of the problem posed by VSA in a particular country and can thus help to assess the efficacy of prevention programmes. Complicating factors are the many possible circumstances which may lead to death, and the fact that, since the International Classification of Diseases (ICD) does not have a category specifically for VSA-related sudden death, it is necessary to collect data on such deaths separately.

The precise mechanism of VSA-related sudden death is seldom clear, but indirect effects such as trauma, aspiration of vomit and asphyxia associated with the use of a plastic bag predominate in deaths associated with solvents from adhesives. In contrast, "direct toxic effects" predominate in deaths associated with fuel gases, aerosols, and chlorinated (and other) solvents. Four modes of "direct" acute VSA-related death can be recognised: anoxia, vagal stimulation leading to bradycardia and cardiac arrest, respiratory depression and the initiation of cardiac dysrhythmias [31]. Of these, cardiac dysrhythmias leading to cardiac or cardiorespiratory arrest are presumed to cause most

deaths. Sudden alarm, exercise or sexual activity may precipitate an arrhythmia since VSA may sensitise the heart to circulating catecholamines; in many VSA-related sudden deaths the immediate ante-mortem event has been said to be fright and running [79,81] or physical struggle [89]. However, this is unlikely to be the whole story since direct toxic effects of 1,1,2-trichlorotrifluoroethane have been described in isolated perfused rat hearts [90].

Chronic toxicity from volatile substance abuse

Chronic sequelae of VSA include recurrent epistaxis, halitosis, oral and nasal ulceration, conjunctivitis, chronic rhinitis, bloodshot eyes, and increased bronchial expectoration. Anorexia, thirst, weight loss and fatigue may also occur. Loss of concentration, depression, lethargy, irritability, hostility and paranoia are further reported complications. In addition, neuropsychological impairment is often present in volatile substance abusers with well-defined neurological abnormalities. Studies have also found that abusers without reported neurological abnormalities obtain lower psychometric test scores than non-abusers, although this may not be caused by VSA but by other factors such as cigarette smoking or the consumption of alcoholic drinks [46,91].

Peripheral neuropathy, cerebellar dysfunction, chronic encephalopathy and dementia have been described after chronic VSA [92]. Chronic abuse of toluene-containing products and of 1,1,1-trichloroethane and trichloroethylene have both been associated with permanent organ damage, especially to the kidney, liver and heart. Lead poisoning from alkyl leads used as antiknock" agents has been reported as a complication of petrol "sniffing" [93–96]. However, since virtually all reports feature case studies or small series of patients referred for treatment, the true incidence of morbidity after VSA is unknown.

Treatment of volatile substance abusers and strategies for prevention

There are significant differences between VSA and some other forms of substance abuse. Firstly, young children are involved to an unusual extent. In many cases, volatile substances may be the first psychoactive substances used. Secondly, in most adolescents VSA is a transient phenomenon, i.e. long-term addiction/habituation to volatiles is relatively rare [97]. However, progression to alcohol and/or illicit drug use has been documented [98,99], although in a recent family study in which 136 solvent abusers were identified, VSA tended to follow alcohol and cannabis use [100]. Some people continue to abuse volatiles for many years [101,102]. In any event, the psychosocial aspects of VSA, for example the disruption caused to the families and friends of abusers [53] and criminal activities performed whilst intoxicated, such as driving a motor vehicle [103], must not be neglected. Finally, there is the ever-present risk of sudden death, probably in part linked to the difficulty of controlling dosage.

In contrast to the situation with illicit drugs, there is in most countries no criminal involvement in supply except perhaps at the level of retailers. Indeed, the almost ubiquitous availability of products which can be abused by inhalation, all of which are relatively safe when used correctly and for their intended purpose, means that it is virtually impossible to control the practice by controlling the availability of abusable products. One suggestion is to label wholesale packs of abusable products (LPG cigarette lighter refills, for example) to warn retailers of the dangers of abuse of the product in question and thus the need to monitor purchases by schoolchildren and adolescents. Labelling the wholesale pack and not the product itself would have the advantage of not drawing the abuse potential of the product to the attention of prospective abusers.

Early recognition of individual problems by health professionals and by the abusers themselves is important if treatment is to be successful. Indeed, the best approach seems to be to prevent individuals from becoming abusers in the first place [104]. In this regard, the main effort in the UK has been in education, not only of school children and their parents and teachers, but also of retailers and health care professionals. Education packs for use in schools and in the community [105] and monographs aimed at health care professionals [106,107] have been produced. A detailed framework for a "solvent abuse (prevention) programme" has been published [25]. Reformulation of abusable products should also be considered. In the UK, for example, only some 20% of sales of contact adhesives are now of solvent-based as opposed to water-based products, compared with more than 50% of sales 10 years ago. The move away from solvent-based adhesives has been stimulated as much by a desire to reduce occupational and domestic exposure to solvents such as toluene as by concerns about VSA.

In Britain, legislation aimed at restricting supply has been enacted in the last 10 years, although various other legislative measures have been invoked to deal with intoxicated abusers [108]. In Scotland, which has its own legal system, The Solvent Abuse (Scotland) Act of 1983 defines the offence of "recklessly" selling solvents to children. In certain cases (such as solvent abuse) children who are thought to be in need of care and protection may be referred to Children's Panels rather than to court. In the period 1983 to 1991, 3487 such referrals were made [109]. In England and Wales, the Intoxicating Substances (Supply) Act of 1985 made it an offence to sell, or to offer for sale, substances to children under the age of 18 years if the vendor knows or has grounds for believing that those substances are likely to be inhaled to achieve intoxication [110].

Whatever preventative strategies are adopted it is important at least to attempt to monitor their effects. For example, the increase in sudden deaths in the UK in recent years is mainly due to an increase in deaths from abuse of LPG and other very volatile substances. It is possible that this could have been caused by undue emphasis on prevention of glue sniffing *per se* whilst neglecting the dangers of abuse of products such as LPG cigarette lighter refills. However, worry that glue sniffing might be detected from stained clothing or from the characteristic smell of solvent may have been a further factor [51].

CLINICAL TOXICOLOGY OF VOLATILE COMPOUNDS

The severity of poisoning depends on the toxicity of an agent and on the magnitude, duration and (sometimes) the route of exposure. Factors such as age and the presence of disease may also be important. In general, the acute CNS depressant and cardiotoxic effects of inhalational anaesthetics and other volatile substances are similar, being related more to their physical properties than to their chemical structure [111]. On the other hand, manifestations of toxicity such as peripheral neuropathy and hepatorenal damage usually result from metabolic transformation and can thus differ markedly between compounds with similar chemical structures.

Acute poisoning

Inhalation of vapour. The clinical features of VSA as well as the risk of sudden death have been discussed above. The inhalation of high concentrations of petrol vapour, such as may be encountered by workmen cleaning storage tanks, may also cause sudden death, either from acute respiratory failure or by precipitating ventricular fibrillation. In the case of chlorinated hydrocarbons, CNS depression was the most common finding in 384 industrial accidents involving inhalation of tetrachloroethylene, 1,1,1-trichloroethane or trichloroethylene; only 17 patients died but 168 more were unconscious when first examined [63]. In contrast, cardiac arrhythmias are thought to be relatively common after abuse of these agents.

With VSA, opportunities to intervene in the acute phase of intoxication are rare but, if the opportunity arises, care must be taken not to further stress or excite the individual concerned because of the risk of inducing a cardiac arrhythmia. In all cases, exposure must be stopped either by taking away the source of intoxication, or removing the individual from the contaminated atmosphere. Supplemental oxygen may be needed and cardiopulmonary resuscitation should be attempted in the event of ventilatory and/or cardiac arrest. Cardiac arrhythmias should be managed conventionally, with special attention being paid to correction of hypoxemia and hypokalemia. Supportive treatment will be needed should renal or hepatic failure develop.

Acute poisoning with carbon tetrachloride is rare and usually results from ingestion or, more rarely, accidental inhalation rather than VSA [112]. The early features of poisoning are similar to those associated with other solvents although cerebellar dysfunction has also been reported [113]. However, ingestion or dermal absorption of as little as 5 to 10 ml of carbon tetrachloride can cause hepatorenal damage and early N-acetylcysteine may be beneficial [114]. Acute exposure to chloroform may also cause hepatorenal damage [115] and N-acetylcysteine may again be beneficial [114].

Methanol poisoning arising from the deliberate inhalation of a dichloromethane/methanol/toluene mixture by a 17-year-old male has been claimed but the evidence is equivocal [116]. The patient was lethargic on admission with

slurred speech and ataxic movement. However, the admission blood methanol concentration was only 0.23 g/l and there were no biochemical or clinical features of methanol toxicity. Moreover, the blood carboxyhemoglobin (HbCO) was only 3% on admission. If occupational exposure to dichloromethane was a possibility, 3% HbCO would be considered insignificant [117]. Blood toluene and dichloromethane were not measured.

Solvent ingestion. Gastrointestinal symptoms may predominate after solvent ingestion, but the later features are similar to those following inhalation of vapour. However, blood concentrations associated with particular features tend to be lower after inhalation as compared to ingestion, probably reflecting more rapid distribution to the CNS after inhalation. Rhabdomyolysis, myoglobinemia and renal failure have been described following ingestion of toluene by a volatile substance abuser [118]. Coma and severe metabolic acidosis of unknown etiology after butanone ingestion have been reported [119]; metabolic acidosis has not been reported after inhalation of this compound and may reflect the relatively large amount absorbed in this latter case.

Gastric lavage, if indicated, must be performed carefully to minimise the risk of aspiration and is contraindicated after petrol ingestion because of the risk of chemical pneumonitis. The management of hydrocarbon ingestion has been reviewed recently [120]. Treatment of acute solvent poisoning by hyperventilation has been advocated [121] but may disturb acid-base balance and cerebral blood flow. In addition, it is difficult to justify sedation and intubation of conscious patients, or intubation of unconscious patients with adequate respiration, followed by mechanical ventilation because these procedures are not without morbidity.

Chronic toxicity

When assessing the possible hazards of chronic VSA, data from studies of occupational exposure to volatile substances are of some relevance, and *vice versa*. However, gathering data other than in the form of case reports is very difficult. Even then assessment of the duration and intensity of the abuse and the products/substances used relies largely on evidence from the patient. Toxicological analysis on admission does not provide evidence of the compound(s) abused in the past. Similarly, studies of occupational exposure to volatiles are fraught with difficulties, not least in some instances the suspicion from the workforce themselves coupled with sometimes grudging cooperation from management. Some of the issues concerning occupational/environmental exposure to solvents have been reviewed [122–124].

In general, volatile substance abusers tend to be young people who expose themselves to massive doses of, at most, a few compounds for relatively short periods, albeit frequently. In contrast, occupational exposure is normally to relatively low concentrations of a variety of substances over many years in an older population, some of whom may have consumed alcohol and/or smoked tobacco throughout their working lives [125]. Nevertheless, some of the obser-

vations made in occupationally-exposed groups presage those now being made in volatile substance abusers such as chronic impairment of cognitive function [126–129].

It might be expected that repeated exposure to virtually anaesthetic concentrations of volatile compounds would to lead to permanent damage of one sort or another. However, this may be hard to detect after VSA because users are generally young and otherwise healthy, with considerable physiological reserve. In spite of these considerations, chronic abuse of toluene-containing products and of 1,1,1-trichloroethane and trichloroethylene have all been associated with permanent organ damage, especially of the kidney, liver and heart. In addition, peripheral neuropathy, cerebellar dysfunction, chronic encephalopathy and dementia have been described. More recently, persistent electroencephalographic disturbances have been described in adolescent "glue sniffers" [130]. However, apart from peripheral neuropathy, which is usually described in association with hexane or 2-hexanone [8,131], a definite causal relationship has been difficult to establish [82]. The mechanism underlying the reported potentiation of hexane neuropathy by butanone [132,133] remains uncertain [134]. Peripheral neuropathy and myelo-neuropathy have also been described following nitrous oxide exposure [9,135] and muscular atrophy with normal sensory function has been attributed to hexane [136]. Schizophrenia has been associated with petrol inhalation [137].

Recently, increases in the rate of chromosome abnormalities and in the frequency of sister chromatid exchange have been reported in a small population of chronic volatile substance abusers [138]. Analogous results have been reported in acutely intoxicated children [139] but it is not clear if the same patients were studied. Similar effects have been attributed to occupational exposure to solvent vapour [140]. The results of Salamanca-Gómez et al. [138,139] are by no means conclusive [141], particularly since other factors, notably cigarette smoking, can cause chromosome damage of the type described. Moreover, there is no evidence that an excess of chromosome aberrations in the lymphocytes of workers exposed to toluene translates into an excess of tumours or deaths from malignant disease [142].

A further consideration is the possible presence of benzene and/or 1,3-butadiene in the products abused. The concentration of benzene in toluene is normally strictly limited and, in the UK, it is present at concentrations much less than 1% (w/w). However, the benzene content of some unleaded petrols has changed recently as a result of measures taken to increase the octane rating, and benzene may now be present at concentrations of 2 to 5% (w/w) in the UK, as in the US [143]. Methyl tert.-butyl ether may also be added at concentrations up to 10% (w/w), again to enhance the octane rating. Thus, although no longer at risk from chronic lead poisoning, abusers of this type of petrol may be faced with a different hazard, perhaps resulting in blood dyscrasias [2]. 1,3-Butadiene is a potent carcinogen in mice [144] and a possible carcinogen in humans [145,146]. 1,3-Butadiene may legally be present in LPG intended for fuel use at concentrations of up to 0.1% (v/v) in the UK. Measurement of haemoglobin

adducts (resulting from binding of 1,2-epoxy-3-butene, the primary metabolite of butadiene) is a potential means of quantitating 1,3-butadiene exposure [147,148].

Clinical sequelae of chronic toluene exposure

There are many reports of chronic toxicity following toluene abuse. However, this may only reflect the prevalence and relatively low risk of sudden death associated with the abuse of this compound, or the fact that toluene is relatively easy to detect in blood. The possible role of impurities such as benzene and of other solvents present in the product abused, for example hexane and methanol [149,150], should also be remembered when evaluating such reports. Some longer term health effects [151] and the reproductive and developmental toxicity [152] of toluene have been reviewed.

Central nervous system. Grabski [153] described cerebellar degeneration due to toluene and there have since been many similar reports [154–157]. In some instances cerebellar degeneration has been associated with cerebral cortical and brainstem atrophy [158]. Acute encephalopathy was described in 19 toluene abusers who presented with behavioural disturbances, ataxia, diplopia, coma and convulsions; one patient still had cerebellar ataxia a year later despite abstinence from toluene [159]. Cerebral cortical atrophy on computerised tomographic (CT) scans was reported in 6 of 11 subjects with toluene exposures of 10 years or more [160]; at least two also had cerebellar atrophy. Clinically, the severity of disease correlated with the duration of exposure. Early features of toxicity included tremor, disturbed thought and amnesia. In another report, a 28-year-old male with a ten-year history of toluene abuse and behavioural disturbance was found dead in bed with a plastic bag and a nearly empty can of toluene. Autopsy suggested cerebral and cerebellar damage, and also abnormal spermatogenesis [161]. Neurophysiological signs of brain damage after toluene abuse have also been reported [152].

Streicher et al. [102] reported 25 patients aged 18 to 40 years who were admitted to hospital after deliberately inhaling fumes from paints or other toluene-containing products (6 to 7 hours/day) for 4 to 14 days prior to admission. The patterns of presentation were: (i) muscle weakness (n = 9); (ii) gastrointestinal complaints, including abdominal pain and haematemesis (n = 6); and (iii) neuropsychiatric disorders, including altered mental status, cerebellar abnormalities and peripheral neuropathy (n = 10). The mean serum potassium concentration in the group with muscle weakness was 1.7 mmol/l (normal range 3.5 to 4.5 mmol/l) and six of eight patients had evidence of rhabdomyolysis (creatine phosphokinase 118 to 4350 IU/l; normal ranges <50 IU/l in women and <85 IU/l in men). Four patients were quadriplegic, two of whom were admitted with an initial diagnosis of Guillain-Barré syndrome, and 18 had renal abnormalities with hematuria, albuminuria and pyuria. The muscle weakness and the gastrointestinal complaints resolved after abstinence from toluene (1–3 days) and fluid and electrolyte replacement.

Cerebellar signs were detected in 11 of 24 toluene abusers admitted to a drug treatment unit [163]. The severity of cerebellar signs correlated inversely with the width of the cerebellar sulci and superior cerebellar cisterns on the CT scan. At least two patients in this study were said to have peripheral neuropathy, even though this is very rare clinically in toluene abusers. Mild sensory peripheral neuropathy, in addition to cerebral and cerebellar atrophy, has also been reported [164]. Despite the clinical rarity of peripheral neuropathy in toluene abusers, it is noteworthy that subclinical impairment of the peripheral as well as the central nervous system has been demonstrated using somatosensory evoked potentials in workers occupationally exposed to toluene [165].

Hormes et al. [155] recorded cerebellar signs in 9 of 20 toluene abusers, seven of whom were also demented. Other features included cranial nerve abnormalities such as anosmia and hearing loss, nystagmus, arm incoordination and spasticity in the legs. The CT scans in eight of these nine patients showed diffuse cerebral and cerebellar atrophy, with brainstem atrophy in the more severe cases. There was no obvious correlation between the neurological signs and the duration of exposure. Symptomatic improvement was noted after abstinence for 1 to 22 months. In one case, neurological improvement after 18 months abstinence was not accompanied by reversal of structural changes noted on serial magnetic resonance imaging (MRI) scans, suggesting irreversibility of toluene-associated cerebral and cerebellar injury.

Diffuse CNS white matter changes were also noted in five of these cases and in two additional patients [166]. Filley et al. [167] studied 14 chronic toluene abusers with the aid of a comprehensive neuropsychological evaluation and cerebral MRI scans. Eight of 14 were found to have evidence of dementia, the degree of which correlated closely with the extent of white matter abnormality noted on MRI. It has been postulated that this is due to the relatively high lipophilicity of toluene and the high concentrations that consequently arise in central white matter [168].

In addition to cerebral and cerebellar atrophy, optic atrophy with blindness and sensorineural hearing loss occurred in a 27-year-old male with a five-year history of toluene abuse [169]. Sensorineural hearing loss, optic atrophy and global brain damage have also been reported in a 27-year-old female glue "sniffer" [170]. A specific ototoxic effect of toluene has been confirmed in animals. In rats, hearing loss, due to an effect on the hair cells in the cochlea, affects certain frequencies only and is concentration, duration and exposure-schedule dependent [171].

Weda et al. [172] also reported optic neuropathy caused by glue-sniffing. More recently, Maas et al. [173] described acquired pendular nystagmus with horizontal and vertical components in four patients who had sniffed glue containing toluene for between 5 and 20 years. Visual abnormalities may be more subtle, however. Holló and Varga [174] reported residual disturbances in colour discrimination after six months of abstinence in five 18- to 20-year-olds who had previously abused glues and solvents of high toluene, xylene and acetone content for several hours daily over a period of three to four years.

Choreoathetosis, grand-mal epilepsy and opisthotonos after toluene abuse in a patient with a five-year history of VSA have been reported [175]. Status epilepticus and convulsions after toluene abuse have been recorded by others [176–178]. Convulsions have also been associated with the abuse of xylene [179].

Histological changes in the cerebellum, apparently induced by toluene, have included loss of neurones, replacement of the Purkinje fibres by diffuse gliosis, and axonal degeneration [164]. Arlien-Soborg et al. [180] suggested that early symptoms of encephalopathy may be due to a reduction in cerebral blood flow because of solvent-induced reduction in cerebral metabolism, which might eventually lead to cerebral atrophy. In this latter study, nine painters were all thought to show some intellectual impairment; the CT scans showed minor or no cerebral atrophy although 19% showed reduced cerebral blood flow. Moen et al. [181] have suggested that solvent-induced chronic toxic encephalopathy may be the result of membrane destabilisation, based on a finding of reduced free taurine (a membrane stabiliser) concentrations in the cerebrospinal fluid of 16 patients with this condition.

Hepatorenal system. Mild fatty liver disease has been described in print workers without other risk factors for liver disease after occupational exposure to toluene [182]. Toluene may have been responsible for serious hepatorenal damage in a 19-year-old male who had abused a cleaning fluid containing 80% (v/v) toluene for 3 years [183].

Metabolic acidosis with a normal anion gap, attributed to distal renal tubular acidosis, was first described in association with toluene abuse by Taher et al. [184]. Subsequently, more evidence associating toluene abuse and renal toxicity has accumulated [185–189]. The patients with renal tubular acidosis described by Taher et al. [184] presented with a combination of muscle weakness, nausea, vomiting and neuropsychiatric disturbances. The muscle weakness may be explained by electrolyte disturbances (hypokalemia and/or hypophosphatemia), although toluene itself may be directly toxic to muscle membranes [102] because serum potassium and phosphate concentrations are not always abnormal. High anion gap acidosis and other metabolic abnormalities have also been described after chronic toluene abuse [102,190–192] and of xylene [193]. Severe acidosis is usually corrected by the administration of sodium bicarbonate but mild acidosis typically resolves without treatment.

The precise mechanism by which toluene and xylene cause metabolic acidosis is not known. It has been suggested that the high anion gap may be due to accumulation of hippuric or benzoic acids, or their methylated derivatives in the case of xylene [194]. Acidosis with no anion gap may be due to impaired generation of the hydrogen ion gradient in distal renal tubules, possibly due to functional damage to the tubular epithelium, or to inhibition of cellular metabolism [195]. This may be compounded by the need to excrete the principal toluene metabolite, hippuric acid, as a water-soluble salt. However, not all cases are due to renal tubular acidosis. Carlisle et al. [196] have emphasised that in six of eight toluene abusers with acidosis but no anion gap reported in

the literature, the urinary ammonium ion excretion was normal. Thus the urinary excretion of hippurate unmatched by ammonium necessitates the excretion of other cations such as sodium or potassium. Continuing potassium loss would lead to hypokalemia, whilst sodium loss would lead to a fall in the extracellular fluid volume and a reduced glomerular filtration rate. This could in turn transform a normal anion gap acidosis into a high anion gap acidosis as hippurate and possibly benzoate accumulate.

Be all this as it may, hypercalcemia and hypercalciuria may result from loss of bone salts during the metabolic acidosis and there is a tendency for renal calculi to form. This propensity for stone formation may be exacerbated by the fact that relatively alkaline urine decreases the solubility of calcium salts, particularly calcium phosphate [197]. Although abstinence may allow features of toxicity to subside, irreversible renal damage in toluene abusers has been reported. Thus, acute renal failure occurred in a 20-year-old in whom serial biopsies failed to show vascular or glomerular changes but did demonstrate persistent tubulo-interstitial abnormalities; the patient remained anuric at 70 weeks [198]. An association between occupational exposure to hydrocarbon mixtures and chronic glomerulonephritis is well described [199–201]. Progressive glomerulonephritis has now been recorded in chronic toluene abusers [202–204]. Interstitial nephritis due to toluene abuse has also been described [205].

Cardiorespiratory system. Chronic toluene inhalation has been associated with lung damage. Respiratory function tests have revealed significantly larger residual volumes among a toluene-abusing population compared with a control group; no significant association was found with age, years of solvent abuse or concomitant use of cigarettes and/or cannabis [206]. Similar findings have been reported after deliberate inhalation of toluene-based spray paints [207]. Autopsies of three toluene abusers revealed abnormal lung morphology consistent with emphysema. Other pulmonary abnormalities, including reduced diffusion capacity and pulmonary hypertension, have been noted [208]. Goodpasture's syndrome in a 17-year-old girl has been reported in association with glue "sniffing" [209]. Dilated cardiomyopathy requiring cardiac transplantation after two years of toluene abuse occurred in a 15-year-old boy [210]. Cardiomyopathy and myocardial degeneration after abuse of toluene and other agents by adults have been noted [211,212].

Hematological. Non-lymphocytic leukemia, although normally associated with benzene, has been noted in a toluene abuser [213]. Fatal bone marrow aplasia attributed to toluene abuse has also been reported [204].

Reproductive and developmental toxicity. A "fetal solvent syndrome" was described in a child of a 20-year-old toluene abuser. The child was small with microcephaly, a flat nasal bridge and a hypoplastic mandible, and exhibited jerky movements from days 2 to 4 which then disappeared spontaneously [215]. There have been subsequent reports of "toluene embryopathy", characterised by microcephaly, CNS dysfunction, attentional deficits and hyperactivity, developmental delay with language deficits, minor craniofacial and limb

anomalies, and variable growth deficiency [216,217]. Congenital renal tubular dysfunction associated with maternal VSA has also been noted [208].

Toluene abuse during pregnancy has been associated with increased maternal and foetal morbidity and foetal mortality. A study of 30 pregnancies in ten women who chronically "sniffed" glue or paint fumes demonstrated that renal tubular acidosis, which occurred in over half the mothers, placed them at risk of hypokalemia, with associated cardiac dysrhythmias and rhabdomyolysis [219]. Amongst 21 neonates exposed to toluene *in utero*, preterm delivery, perinatal death and growth retardation were significantly increased.

Clinical sequelae of chronic exposure to chlorinated solvents

Chronic exposure to trichloroethylene and to 1,2-dichloropropane has been associated with hepatorenal damage [220–223]. Convulsions and cerebral infarction [224], congestive cardiomyopathy [225,226] and pulmonary oedema [227] have also been reported with trichloroethylene, and a grand-mal convulsion after abuse of monochloroethane has been described [228]. However, the possible contribution of more toxic solvents is not known since no toxicological analyses were performed. Similarly, hepatorenal damage attributed to tetrachloroethylene [229] and 1,1,1-trichloroethane [230] may have been due to more toxic compounds such as carbon tetrachloride or chloroform present as impurities.

Nevertheless 1,1,1-trichloroethane exposure has been associated with the development of Goodpasture's syndrome [231] and four patients with fatty liver disease attributed to occupational exposure to 1,1,1-trichloroethane have been reported [232]. Cranial neuropathy has been described after trichloroethylene exposure [233]. Parkinsonism has been reported in association with chronic exposure to carbon tetrachloride [234]. Moreover, a collaborative multicentre European study of the renal effects of occupational exposure to tetrachloroethylene in dry cleaners found significant biochemical and immunochemical abnormalities compared to controls, suggesting diffuse structural and functional changes within the kidney [235]. These changes may have resulted from generalised membrane disturbances caused by the compound itself or by reactive metabolites.

DIAGNOSIS OF POISONING DUE TO VOLATILE SUBSTANCES

Clinical and circumstantial evidence

Many of the problems associated with VSA may appear similar to the normal problems of adolescence [24]. However, VSA should be suspected in children and adolescents with "drunken" behaviour, unexplained listlessness, anorexia and moodiness. The hair, breath and clothing may smell of solvent, and empty adhesive tubes or other containers, potato crisp bags, cigarette lighter refills,

or aerosol spray cans are often found. The smell of solvent on the breath is related to the dose and duration of exposure and may last for many hours. The so-called "glue-sniffer's rash" (perioral eczema) is caused by repeated contact with glue poured into a plastic bag. However, in one study only 2 of 300 children who regularly "sniffed" glue were found to exhibit this feature [236]. It is especially important to consider all circumstantial evidence in cases of possible VSA-related death since suicide or even homicide cannot be excluded simply on the basis of the toxicological examination. Although not strictly VSA, death in association with "torch breathing", i.e. igniting inhaled fuel gas (propane in this instance), which resulted in a flash fire, has also been described [43]. The patient did not suffer burns. Propane was detected in blood and lung tissue.

Role of toxicological analyses

Instances where an analytical toxicology laboratory may be asked to perform analyses for solvents and other volatiles in biological samples and related specimens include (i) the clinical diagnosis of acute poisoning; (ii) confirmation of suspected chronic VSA in the face of denial from the patient and/or a caretaker; (iii) investigation of deaths where poisoning by volatile compounds is a possibility; (iv) investigation of rape or other assault, or other offence such as driving a motor vehicle or operating machinery whilst under the influence of drugs or other agents; (v) investigation of fire or explosion where VSA might have been a contributory factor; and (vi) assessment of occupational or environmental exposure to solvent vapour.

Experience in the UK has shown that VSA-related deaths can easily be overlooked if sudden deaths in children and adolescents are not investigated thoroughly. Post-mortem examination usually reveals little except perhaps acute lung congestion and possibly burns to the mouth and throat. A further factor is that well-meaning friends or parents may remove circumstantial evidence of VSA (product abused, plastic bag) from the scene prior to an investigation. Techniques other than the measurement of the volatile substance in blood such as ambient air monitoring or the measurement of urinary metabolite excretion may be more appropriate after occupational exposure.

The analysis of biological samples for solvents and other volatiles which may be abused by inhalation has clear parallels with the analysis of methanol, ethanol and 2-propanol. Headspace GC is widely used for this latter analysis, and this same technique provides a viable method for the analysis of volatiles such as solvents in blood and other biological specimens which may be obtained without using special apparatus such as breath-collection tubes [13,237]. Direct mass spectrometry of expired air can also detect many compounds several days post-exposure. However, the use of this technique is limited by the need to take breath directly from the patient [238]. Vapour-phase infra-red spectrophotometry may be useful in the analysis of abused products [239].

Sample collection and storage. Whole blood is the best sample for analysis of solvents and other volatile substances since many such compounds

are concentrated in erythrocytes [240]. An anticoagulant (lithium heparin) should be used. Many volatile compounds are relatively stable in blood if simple precautions are taken. The container should be glass or hard plastic, preferably with a cap lined with metal foil. The tube should be as full as possible and should only be opened when required for analysis and then only when cold (+4°C) [241]. If the sample volume is limited it is advisable to select the container to match the volume of blood so that there is minimal headspace. Specimen storage between –5 and +4°C is recommended and, in the case of esters such as ethyl and methyl acetates, 1% (w/v) sodium fluoride should be added to minimise esterase activity. However, many samples submitted in far from ideal circumstances still give useful qualitative results.

Products thought to have been abused should be packed, transported and stored entirely separately from biological specimens to avoid cross-contamination. In a suspected VSA fatality, analysis of tissues (especially fatty tissues such as brain) may prove useful since high concentrations of volatile compounds may be present even if very little is detectable in blood. Tissues should be stored before analysis in the same way as blood. Analysis of urine may also be useful if the abused compound is broken down *in vivo*.

Pharmacokinetics of volatile substances

Some knowledge of the pharmacokinetics of volatile compounds is important in understanding the rate of onset, the intensity, and the duration of intoxication with these substances, as well as the rate of recovery. Such an understanding is also helpful when attempting to interpret the results of toxicological analyses performed on biological samples from poisoned patients. The physical properties and pharmacokinetic parameters of some volatile substances are summarised in Table 23.5. These parameters have been studied extensively in the context of occupational exposure [245–247] and anaesthesia [242] but not in relation to VSA. These three situations are similar in that dosage (though sometimes variable, especially during occupational exposure and VSA) is often prolonged.

Absorption, distribution and elimination. The major factors influencing pulmonary uptake of a given solvent during chronic (occupational) exposure have been summarised [248] and include:

(a) The concentration of the compound in inspired air.

(b) The air:blood and blood:tissue partition coefficients.

(c) Pulmonary ventilation and blood flow (respiratory rate, fitness, exercise).

(d) The proportion of body fat (this may be as high as 50% of body weight in obese individuals).

(e) Work practices (adequacy of workplace ventilation).

(f) Interaction with other inhaled compounds, drugs or alcohol.

(g) Addiction or aversion to the compound.

(h) Individual variation in metabolic clearance.

Compound[1]	MEL/ OES (ppm)	Inhaled dose absorbed (%)	Proportion absorbed dose		Half-life[2] (h)	Brain:blood distribution ratio	Partition coefficient blood:gas (37°C)
			Eliminated unchanged (%)	Metabolised (%)			
Acetone	750	–	–	–	3–5[3]	–	243–300
Benzene	5	46	12	80	9–24	3–6	6–9
Butane	1000[4]	30–45	–	–	–	–	–
Isobutane	1000[4]	–	–	–	–	–	–
Butanone	200	70	99+	0.1	0.5	–	116
Carbon disulphide	10	40	<30	50–90	<1	–	2.4
Carbon tetrachloride	2	–	50?	50?	48	–	1.6
Chlorodifluoro-romethane	1000	–	–	–	–	1.9	–
Chloroform	2	–	20–70 (8 h)	>30	1.5	4	8
Cyclopropane	–	–	99	0.5	–	1.5–3.6	0.55
Dichlorodifluoro-romethane	1000	35	99	<0.2	–	1.4	0.15
Dichloromethane	100	–	50?	<40	0.7	0.5–1	5–10
Diethyl ether	400	–	>90	–	–	1.1	12
Enflurane	20[5]	90+	>80 (5 d)	2.5	36	–	1.9
Ethyl acetate	400	–	–	–	–	–	–
Halothane	10[5]	90+	60–80 (24 h)	<20	0.5	2–3	2.4
Hexane	20	–	–	–	–	–	–
Isoflurane	50[5]	–	–	–	–	–	–
Methoxyflurane	–	–	19 (10 d)	>44	–	2–3	11
Methyl isobutyl ketone	50	–	–	–	–	–	–
Nitrous oxide	100[5]	–	>99?	–	–	1.1	0.47

Compound[1]	MEL/ OES (ppm)	Inhaled dose absorbed (%)	Proportion absorbed dose		Half-life[2] (h)	Brain:blood distribution ratio	Partition coefficient blood:gas (37°C)
			Eliminated unchanged (%)	Metabolised (%)			
Propane	1000[4]	–	–	–	–	–	–
Styrene	100	–	1–2	>95	13	–	32
Tetrachloroethylene	50	60+	>90	1–2	72	9–15	9–19
Toluene	50	3	<20	80	7.5	1–2	8–16
1,1,1-Trichloroethane	350	–	60–80 (1 w)	2	10–12	2	1–3
Trichloroethylene	100	50–65	16	>80	30–38	2	9.0
Trichlorofluoro-methane	1000	92	89	<0.2	1.5	2.5	0.87
Xylene	100	64	5	>90	20–30	–	42.1

1 UK Maximum Exposure Limit/Occupational Exposure Standard (8 h time weighted average) (see Ref. [244]).
2 Terminal phase elimination half-life.
3 Longer after high doses.
4 As components of liquified petroleum gas (LPG).
5 From 1 January 1994.

Table 23.5. *Physical properties and pharmacokinetic data of some volatile compounds (adapted from Refs. [117,242,243])*

The potential complexity of the situation is illustrated by a report on the effect of ethanol ingestion on toluene uptake in 11 subjects: although the total uptake of toluene was decreased, the maximum blood toluene concentration was increased and the apparent clearance decreased [249].

It is useful to model the pharmacokinetics of volatile compounds to help understand the complex processes occurring *in vivo*. A water tank/pipe model is useful [250]. Here, the tanks represent groups of organs/tissues (compartments) and the diameters of the inter-connecting pipes illustrate the ability of the compound to move between compartments (blood supply). Thus, the brain, heart, liver, kidney and gut have a small storage capacity (small tank) but a large systemic blood flow (wide pipe). Muscle, in contrast, has a large capacity (large tank) but a lower blood supply (narrow pipe) while adipose tissue has a very large capacity to store non-polar compounds (very large tank) but a very poor blood supply (very narrow pipe).

It follows that inhaled compounds may rapidly attain high concentrations in vital, well-perfused organs (brain, heart) while concentrations in muscle and adipose tissue may be low. Should death occur, this situation is "frozen", but if exposure continues the compound will slowly accumulate in less well perfused tissues, only to be slowly released once exposure ceases. Thus, the plasma concentrations of some compounds may fall monoexponentially, while others may exhibit two (or more) phases of decline (half-lives). Published data on the elimination half-lives of volatile substances are not easily comparable, either because too few samples were taken or the analytical methods used did not have sufficient sensitivity to measure the final half-life accurately.

UK Maximum Exposure Level (MEL) or Occupational Exposure Standard (OES) data (Table 23.5) provide information on the relative toxicities of different volatile compounds. The partition coefficients of a number of compounds between air, blood and various tissues have been measured *in vitro* using animal tissues [242], and some *in vivo* distribution data have been obtained from post-mortem tissue measurements in human fatalities (Table 23.5). However, these latter data must be used with caution since there are many difficulties inherent in such measurements such as sampling variation, analyte stability, and the use of external calibration.

Metabolism. Many volatile substances are eliminated unchanged in exhaled air. Others are partly eliminated in exhaled air and also metabolised in the liver and elsewhere, the metabolites being eliminated in exhaled air or in urine (Table 23.6). After ingestion, extensive hepatic metabolism can reduce systemic availability ("first-pass" metabolism). The pharmacological activity and pharmacokinetics of any metabolite(s) often differ from those of the parent compound(s). Exogenous compounds may be metabolised in a number of ways, a frequent result being the production of metabolites of greater polarity (water solubility) and thus lower volatility than the parent compound. As with other exogenous compounds, Phase I reactions (usually oxidation, reduction or hydrolysis) and Phase II reactions (conjugation with glucuronic acid, sulphate, acetate or an amino acid) occur with certain solvents. The rate and

extent of metabolism may be affected by factors such as age, disease, dose and exposure to other drugs or solvents. Ingestion of paracetamol, for example, has been reported to increase blood toluene concentrations [258], whilst ethanol ingestion inhibits mandelic acid excretion after exposure to styrene [259].

Methyl and ethyl acetates are rapidly hydrolysed to the corresponding alcohols and acetate. Aromatic hydrocarbons such as toluene and xylene are metabolized largely by oxidation on the side chain(s) and conjugation with glycine. Hydroxylation on the aromatic ring is a minor pathway (Table 23.6). Benzene is metabolized extensively by ring hydroxylation and conjugation. Aliphatic hydrocarbons such as hexane are metabolised by oxidation on secondary carbons. Thus, *in vivo* hexane gives rise to 2-hexanol, 2-hexanone and eventually 2,5-hexanedione (Table 23.6). Of the common chlorinated solvents, dichloromethane undergoes dechlorination whilst trichloroethylene undergoes transchlorination.

Compound	Principal metabolites (% absorbed dose)	Notes
Acetone	2-Propanol (minor) and intermediary metabolites (largely excreted unchanged at higher concentrations)	Endogenous compound produced in large amounts in diabetic or fasting ketoacidosis; also the major metabolite of 2-propanol in man [251,252].
Acetonitrile	Inorganic cyanide (at least 12%) thence to thiocyanate	Cyanide/thiocyanate may accumulate during chronic exposure.
Benzene	Phenol (51–87%), catechol (6%), hydroquinone (2%), *trans,trans*-muconic acid	Excreted in urine as sulphate and glucuronide conjugates. Urinary phenol excretion has been used to indicate exposure but is variable and subject to interference [253].
Bromomethane	Inorganic bromide (and others?)	Serum bromide has been used to monitor exposure although the concentrations associated with toxicity are much lower than when bromide itself given orally.
Butanone	3-Hydroxybutanone (0.1%)	3-Hydroxybutanone excreted in urine. Most of an absorbed dose of butanone is excreted unchanged in exhaled air.
Carbon disulphide	2-Mercapto-2-thiazolin-5-one, 2-thiothiazolidine-4-carboxylic acid (TCCA), thiourea, inorganic sulphate and others	2-mercapto-2-thiazolin-5-one glycine conjugate and TCCA glutathione conjugate of carbon disulphide. Urinary TCCA excretion reliable indicator of exposure [254].
Carbon tetrachloride	Chloroform, carbon dioxide, hexachloroethane and others	Trichloromethyl free radical probably responsible for hepatorenal toxicity.

Table 23.6. *Summary metabolism of some solvents and other volatile substances*

Compound	Principal metabolites (% absorbed dose)	Notes
Chloroform	Carbon dioxide (up to 50%), diglutathionyl dithiocarbonate	Phosgene (reactive intermediate) depletes glutathione and is probably responsible for hepatorenal toxicity.
Cyclohexanone	Cyclohexanol (50%+)	Cyclohexanol excreted in urine largely as glucuronide [255].
Dichloromethane	Carbon monoxide (25–34%), carbon dioxide (70%)	Carbon monoxide half-life 13 h (after inhalation of carbon monoxide, 5 h). Blood carboxyhemoglobin measurement useful indicator of chronic dichloromethane exposure
Dimethylsulphoxide	Dimethylsulphide (3%), Dimethylsulphone (18–22%)	After oral/dermal administration, dimethylsulphide excreted in exhaled air and dimethylsulphone in urine.
Dioxane	β-Hydroxyethoxyacetic acid (HEAA)	HEAA excreted in urine.
Enflurane	Difluoromethoxydifluoroacetic acid (>2.5%) inorganic fluoride	—
Ethyl acetate	Ethanol, acetic acid	Rapid reaction catalysed by plasma esterases.
Ethylbenzene	Methylphenylcarbinol (5%), mandelic acid (64%), phenylglyoxylic acid (25%)	Methyphenylcarbinol excreted in urine as conjugate, others as free acids. Mandelic acid excretion has been used to mitor ethylbenzene exposure.
Halothane	Chlorotrifluoroethane, chlorodifluoroethylene, trifluoroacetic acid, inorganic bromide and others	The formationof reactive metabolites may be important in the aetiology of the hepatotoxicity ('halothane hepatitis') which may occur in patients exposed to halothane [256].
Hexane	2-Hexanol, 2-hexanone, 2,5-hexanedione	2-Hexanol excreted in urine as glucuronide. 2,5-Hexanedione neurotoxic metabolite [83]. Methyl butyl ketone also neurotoxic and also metabolised to 2,5-hexanedione.
Isobutyl nitrite	2-Methyl-1-propanol (99%+), inorganic nitrite	Parent compound not detectable in blood. Blood methemoglobin can be used to monitor exposure.
Isopentyl nitrite	3-Methyl-1-butanol (99%+), inorganic nitrite	Parent compound not detectable in blood. Blood methemoglobin can be used to monitor exposure.
Methanol	Formaldehyde (up to 60%), formic acid	Urinary formic acid excretion has been advocated for monitoring methanol exposure.
2-Propanol	Acetone (80–90%) thence others	2-Propanol half-life ±2 h, acetone half-life ±22 h.
Styrene	Mandelic acid (85%) and phenylglyoxylic acid (10%); hippuric acid may be minor metabolite	Urinary mandelic acid excretion indicates exposure [273].

Compound	Principal metabolites (% absorbed dose)	Notes
Tetrachloroethylene	Trichloroacetic acid (<3%)	Urinary trichloroacetic acid excretion serves only as qualitative index of exposure.
Toluene	Benzoic acid (80%) and ortho-, meta- and para-cresol (1%)	Benzoic acid largely conjugated with glycine giving hippuric acid which is excreted in urine (half-life 2–3 h). Not ideal index of exposure since there are other (dietary) sources.
1,1,1-Trichloroethane	2,2,2-Trichloroethanol (2%) trichloroacetic acid (0.5%)	Urinary metabolites serve as qualitative index of exposure only (compare tetrachloroethyline).
Trichloroethylene	2,2,2-Trichloroethanol (45%) trichloroacetic acid (32%) (and dichloroacetate)	Trichloroethanol (glucuronide) and trichloroacetic acid excreted in urine (half-lives about 12 and 100 h). Trichloroacetic acid excretion can indicate exposure.
Xylenes	Methylbenzoic acids (95%) and xylenols (2%)	Methylbenzoic acids conjugated with glycine and urinary methylhippuric acid excretion used as index of exposure — no dietary sources of methylbenzoates.

Table 23.6. *Summary metabolism of some solvents and other volatile substances (continued)*

Although metabolism normally results in detoxification, enhanced toxicity may also result. This is especially true of solvents and other volatile compounds; aspects of the toxicity of, for example, acetonitrile, carbon tetrachloride, chloroform, dichloromethane, hexane, methanol, trichloroethylene and probably halothane can be attributed to the formation of toxic metabolites. Many other compounds including butane, many fluorocarbons, tetrachloroethylene and 1,1,1-trichloroethane are largely excreted unchanged in expired air.

Interpretation of qualitative analytical data

The likelihood of detecting exposure to volatile substances by headspace GC of blood is determined by the nature of the compound(s) involved, the extent and duration of exposure, the time of sampling in relation to the time elapsed since exposure, and the precautions taken when collecting and storing the sample [241]. In one series of suspected abusers, volatile compounds or metabolites were detected in 79 of 125 cases. In 69 (87%) of positive cases the samples were obtained within 10 h of the suspected exposure. Nevertheless, exposure can be detected using later samples — in separate cases toluene was detected at 40 hours and 2,2,2-trichloroethanol (from trichloroethylene) at 48

hours [67]. Analysis of urinary metabolites may extend the time in which exposure may be detected but, of the compounds commonly abused, only toluene, the xylenes and some chlorinated solvents, notably trichloroethylene, have suitable metabolites (Table 23.6). The diagnosis of chronic petrol "sniffing" has been assisted by measuring blood lead concentrations [260]. The detection of aromatic components of petrol such as toluene and ethylbenzene may also help diagnose acute poisoning [261]. However, with some petrols and other complex mixtures such as petroleum ethers (Table 23.3) blood concentrations of the individual components are often below the limit of detection of headspace GC methods even after massive exposure [262,263].

Detection of a volatile compound in blood does not always indicate VSA or occupational/environmental exposure to solvent vapour. Acetone and some homologues may occur in high concentrations in ketotic patients. Large amounts of acetone and butanone may also occur in blood and urine from children with acetoacetyl CoA thiolase deficiency [264]. In addition, acetone is the major metabolite of 2-propanol in man (Table 23.6). Conversely, 2-propanol has recently been found in blood from ketotic patients [265]. Other ketones may also give rise to alcohols *in vivo*. Cyclohexanol, for example, is the principal metabolite of cyclohexanone in man (Table 23.6). Other volatile compounds such as halothane and paraldehyde may be used in therapy.

Sample contamination with propellant gas may occur if the sample is collected in a room where an aerosol has been sprayed recently. Aerosol disinfectants are a case in point. Contamination of blood samples with ethanol or 2-propanol may also occur if an alcohol-soaked swab is used to cleanse skin prior to venepuncture. Gross contamination with technical xylene (a mixture of ortho-, meta- and para-xylene together with ethylbenzene) has been found in blood collected into Sarstedt Monovette Serum Gel blood collection tubes [266]. Contamination with 1-butanol may also occur in blood collected into tubes coated with ethylene diamine tetra-acetic acid (EDTA). A further compound which may be encountered, chlorobutanol (1,1,1-trichloro-2-methyl-2-propanol), is still sometimes employed as a sedative and also as a preservative [267].

It is well known that ethanol may be both produced and metabolised by microbial action in biological specimens [268]. Propanols and butanols may also be produced by microbial action. Small amounts of hexanal may arise from degradation of fatty acids in blood on long-term storage even at –5 to –20°C [241]. Hexanal is resolved from toluene on the temperature programmed GC screening systems described by Ramsey and Flanagan [237] and by Streete et al. [13], but resolution may be lost if an isothermal quantitative analysis is performed. However, interference from hexanal is only likely to be important if very low concentrations of toluene (0.1 mg/l or less) are to be measured.

The alkyl nitrites which are abused by inhalation (isobutyl nitrite, isopentyl nitrite) are a special case in that (i) they are extremely unstable and break down rapidly *in vivo* to the corresponding alcohols and (ii) usually also contain other isomers (butyl nitrite, pentyl nitrite). Any products submitted for analysis will usually contain the corresponding alcohols as well as the nitrites.

Aspects of the analysis of the alkyl nitrites have been reviewed [117,269]. The profound methaemoglobinemia arising particularly from oral ingestion of these compounds can be easily detected [270].

Interpretation of quantitative analytical data

Some data to aid the interpretation of results in individual cases are given by Baselt and Cravey [117] and Moffat [243]. In very general terms, blood concentrations of volatile substances of 5–10 mg/l and above are associated with clinical features of toxicity. In other words pharmacologically effective concentrations of volatile substances are similar to those of inhalational anaesthetics [117,242], and are thus an order of magnitude lower than those observed in poisoning with relatively water-soluble compounds such as ethanol.

Blood toluene concentrations and clinical features of toxicity. Oliver [271] reported that 50% of patients with blood toluene concentrations between 5 and 10 mg/l showed marked intoxication, and that virtually all patients with concentrations greater than 10 mg/l were comatose or dead at the time of sampling. However, shortly after exposure signs of only moderate intoxication (slurred speech, unsteady movements) have been associated with blood toluene concentrations up to 30 mg/l [272]. Blood toluene concentrations above 9.2 mg/l were associated with impairment or probable impairment in car drivers arrested in Norway in 1983–87 [103]. In an occupational setting, blood toluene concentrations after exposure to up to 127 ppm toluene (UK maximum exposure limit 100 ppm) for 8 h ranged between 0.4 to 6.7 mg/l [273].

Blood toluene concentrations in samples from 132 patients suspected of VSA ranged from 0.2 to 70 mg/l and were in excess of 5 mg/l in 22 of the 25 deaths reported [67]. Although there was a broad correlation between blood concentration and severity of poisoning there were large variations within each patient group; 13 patients with blood toluene concentrations greater than 10 mg/l were either asymptomatic or only mildly intoxicated (headache, nausea, vomiting and drowsiness), although these manifestations of toxicity can lead to "indirect" acute VSA-related death [31]. Similar findings have been reported from Japan [274]. Aside from individual differences in tolerance, and possible loss of toluene from the sample prior to analysis [241], the lack of a strong correlation between blood concentrations and clinical features of poisoning is probably due to rapid initial tissue distribution and elimination.

Some 80% of a dose of toluene is converted to hippuric acid (Table 23.6). Similarly, more than 90% of a dose of xylene is metabolised to methylhippuric (toluric) acids. 3-Methylhippurate is the principal isomer found in urine since meta-xylene is the principal component of technical grade xylene (Table 23.3). Methylhippurates are not normal urinary constituents, but hippuric acid may arise from the metabolism of precursors in foods and medicines, and thus caution is needed in the interpretation of analytical results. Hippurate and methylhippurate excretion are often expressed as a ratio to creatinine since this obviates the need for timed urine collections. Occupational exposure to

toluene can give rise to ratios of 1 g hippurate/g creatinine or more [275]; in patients suspected of VSA a ratio of more than 1 g/g suggests, but does not prove, toluene exposure [67]. Measurement of urinary ortho-cresol has been proposed as an alternative means of monitoring toluene exposure selectively, particularly in occupational circumstances [276], but the assay procedure is relatively complex and is thus not widely used.

Blood 1,1,1-trichloroethane concentrations and clinical features of toxicity. After exposure to 350 ppm (UK maximum exposure limit) for one hour, the mean blood 1,1,1-trichloroethane concentration was 2.6 mg/l [277]. Blood 1,1,1-trichloroethane concentrations ranged from 0.1 to 60 mg/l in samples from 66 VSA patients, 29 of whom died [67]. There was again a broad relationship between blood concentration and the severity of poisoning but there were large variations within each patient group. As with toluene, the absence of a strong correlation between blood concentration and clinical features is probably due to rapid initial distribution into tissues. In addition, other compounds were present in many non-fatal cases, further complicating recognition of any dose-response relationship.

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Human Toxicology, J. Descotes (Ed.)

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24. Alcohols and glycols

INTRODUCTION

This group of poisonings mainly involves patients that have ingested ethanol alone or in combination with other drugs, for example hypnotics and sedatives. Most registrars/residents are familiar with this common condition for which treatment consists primarily of gastric decontamination and supportive care. Many of these patients are heavy alcohol consumers and therefore need special attention as to supplementation with vitamin B_1 (to avoid Wernicke's encephalopathy) and to the possible development of delirium tremens (DT) during the withdrawal period following an acute overdose. In addition, the patient with alcoholic breath and coma should always be checked for possible head injuries as the normal correlation between the blood ethanol level and the breath concentration of alcohol is lacking in these patients.

The problems are exaggerated, even for the experienced clinician, when one (or even more) of the patients admitted as a typical ethanol intoxication happens to be poisoned by some other alcohols or glycols. If the clinician does not have a high alertness to this possibility, a critically ill patient with pronounced metabolic acidosis may result, as is usually the case if methanol or ethylene glycol has been ingested. The literature in this area contains many of these cases, especially considering that the most badly diagnosed or treated cases probably have not been reported.

Another problem results from the ingestion of technical spirits containing different alcohols. Although several toxic alcohols might be ingested, a less toxic alcohol, such as isopropanol or ethanol, may temporarily protect against the effects of more toxic alcohols, such as methanol or ethylene glycol. In such situations, the severe toxicity with metabolic acidosis does not develop until after the "protecting" alcohols are eliminated.

For most practical purposes, the alcohols/glycols can be divided into the following three groups from a therapeutic point of view: (1) ethanol and isopropanol; (2) methanol and ethylene glycol; (3) the other alcohols and glycols.

Due to the high taxes on ethanol-containing beverages in Scandinavia, we have extensive experience in dealing with methanol and ethylene glycol poisonings following ingestion as substitutes for ethanol (intentionally or mistak-

enly). Suicidal ingestions with these alcohols are less common, but these often are the most difficult to treat because of the usually massive ingestion. Over the years, through clinical experience and research, guidelines have been developed for the use of the anion and osmolal gaps whenever approaching (unknown) alcohol or glycol poisonings. We successfully use these guidelines in our department and for inquiries to the National Poisons Information Center. When these guidelines have been followed, we have not missed the diagnosis (false negative) in any case of methanol or ethylene glycol poisoning. In a couple of cases (false positive), an initiated IV ethanol drip had to be discontinued when specific analyses ruled out the presence of methanol or ethylene glycol — an acceptable overtreatment in our opinion.

Use of the anion and osmolal gaps

Calculation of the anion and osmolal gaps should be performed by the clinician whenever facing a metabolic acidosis of unknown origin. In addition to being critical information for diagnosing methanol or ethylene glycol poisoning, familiarity with these parameters also helps the clinician to better understand the complicated area of acid/base and electrolyte disturbances. Use of the anion gap increases the understanding of the Gamble diagram and the use of the osmolal gap aids the user in understanding the SI-units and how this system simplifies many aspects of clinical chemistry. The use of the anion and osmolal gaps for diagnosis of toxic alcohol ingestions should always be accompanied by urine microscopy in order to look for the typical calcium oxalate crystals seen in ethylene glycol intoxications.

Assessment of the anion gap

If a specific analytical method for methanol is not available, the anion gap should be calculated from serum electrolyte concentrations using the formula:

$$\text{Anion gap} = (Na^- + K^+) - (Cl^- + HCO_3-)$$

Since positive and negative charges in blood remain in balance, there is no true anion gap. However, as defined by this formula, the anion gap normally varies between 10–16 mmol/l and is due to negatively charged proteins, mainly albumin, and some fatty acids and inorganic ions [1,2]. In metabolic acidosis with a low bicarbonate concentration and a normal anion gap, the chloride concentration will always be increased, provided there is no gross abnormality of the serum proteins. An acidosis with an increased anion gap and a normal chloride level indicates retention of non-volatile organic acids such as may be present in renal failure, ketoacidosis, lactic acidosis or ingestion of such substances as methanol, ethylene glycol, salicylate or paraldehyde. In the absence of such conditions as circulatory failure, diabetes, alcoholism and uremia, an increased anion gap strongly suggests poisoning with one or more of these substances.

Assessment of the osmolal gap

The osmolal gap (OG) is the difference between the measured (Om) and the calculated osmolality (Oc) in serum, OG = Om – Oc. Normally, sodium (and its accompanying anions), glucose and urea determine the osmolality of serum as expressed by the formula:

$$\text{Calculated osmolality} = (1.86 \times \text{Na} + \text{urea} + \text{glucose}) / 0.93$$

if SI-units are used. If urea and glucose concentrations are determined in mass units (mg/dl) the formula is:

$$\text{Calculated osmolality} = (1.86 \times \text{Na} + \text{urea} / 2.8 + \text{glucose} / 18) / 0.93$$

1.86 is the osmotic coefficient for sodium chloride, and although it may be slightly altered if other anions replace chloride, this is of no practical importance. The formula is based on the amount of water in serum (93%) and altered serum water (such as in hyperproteinemia or hyperlipidemia) may therefore slightly alter the osmolal gap [3,4].

The osmolal gap has been measured as 5 (SD ± 7) mOsm/kg H_2O in an unselected population of acutely admitted patients [2] and consisted mainly of calcium (and its corresponding anions), lipids and proteins. An increased osmolal gap indicates that one or more toxicants are present in high molar concentrations. Most drugs, including salicylates, cannot be identified this way because they are dissociated or do not attain high enough serum concentrations on a molar basis. The toxic substances which are the most likely to increase the osmolal gap, are those with a low molecular weight and that are present in high mass units, i.e. high molar concentrations. The lower alcohols and glycols are among such substances. A methanol concentration of 32 mmol/l (1 g/l) increases the osmolal gap by 32/0.93 = 34 mosm/kg H_2O. The osmolal contribution of methanol is so important that interference from other causes will only occur at low levels of methanol (<0.5 g/l). Only methanol and ethylene glycol regularly cause severe metabolic acidosis and elevation of both the anion and osmolal gaps.

Pitfalls in using the gaps

Serum osmolality measurements must be performed with the freezing point depression method; the vapor pressure method will *not* determine the volatile alcohols.

If ethanol is coingested with methanol or ethylene glycol, metabolic acidosis will not occur until most of the ethanol is metabolized, due to the antidotal effect of ethanol. Thus, the osmolal gap will be marked, but the anion gap would appear normal. In such circumstances, repeated calculation of the gaps will determine when ethanol has been eliminated, as the anion gap will then increase.

When patients are first encountered during the late stages of methanol or ethylene glycol poisonings, most of the alcohol or glycol will already have been metabolized to its acidic metabolites. In this situation, there will be a pronounced metabolic acidosis with a high anion gap. However, due to low alcohol or glycol levels, the osmolal gap may be close to normal values. In such situations, specific diagnosis may require determination of the molecular form of the acid metabolite, i.e. formate, glycolate or something else. Treatment, however, would not be dependent on these latter findings.

ETHYL ALCOHOL

Acute ethanol poisoning is one of the most common medical emergencies. In a prospective study of 1212 poisonings (Oslo 1980 study), analytical analysis showed that ethanol was found the main toxic agent in 19.4% of cases and was also implicated in an additional 34.7% [5]. The presence of ethanol may significantly potentiate the toxicity of numerous co-ingested substances; yet it will delay the development of methanol or ethylene glycol toxicity.

Toxicology and toxicokinetics

Distilled spirits (whisky, gin, vodka) usually contain 40–50% ethanol; wines contain 10–12% ethanol and beer ranges from 2–6% ethanol, while standard lager contains about 4% ethanol. Numerous over-the-counter medicinal or cosmetic products can also contain significant percentages of ethanol (10–40%).

The lethal dose of ethanol is variable and depends upon previous drinking habits (due to tolerance) or upon the presence of organ complications in the alcoholic. Development of tolerance tends to increase the lethal dose and organ complications, while malnutrition tends to decrease the lethal dose. In our experience, the lethal ethanol dose for adults is about 3–5 g/kg in adults (75 kg), corresponding to a lethal serum concentration of 5–8 g/l (110–180 mmol/l). Chronic alcohol abusers may die with relatively low blood ethanol concentrations (2.5–4 g/l; 54–87 mmol/l) even when no other drugs are detected analytically. These fatalities may be related to alcohol-induced organ complications, such as cardiomyopathy and malnutrition, or to development of secondary infections, of which pneumonia is the most common. The lethal dose in children is significantly lower, about 1.5–3 g/kg, because of the greater potential for hypoglycemia. Non-tolerant adolescents having their first experience of ethanol may be severely poisoned even at blood ethanol levels of 1 g/l (22 mmol/l) and may develop hypotension or coma.

The highest reported blood ethanol concentration in a surviving patient, 11.3 g/l (245 mmol/l), was found in a 65-year-old male following the suicidal ingestion of two and a half bottles of whisky over several hours [6]. Despite cardiac arrest, disseminated intravascular coagulation, and acute renal failure, the patient survived with no latent sequelae. A blood ethanol concentration of 7.8

g/l (169 mmol/l) was reported in a young woman with no symptoms other than moderate CNS depression, which illustrates the importance of tolerance and interindividual variability when interpreting blood ethanol concentrations [7]. In children, survival has been reported with blood ethanol levels as high as 4.6 g/l (99 mmol/l) in a 30-month-old boy (13 kg) [8]. The survival of patients with very high blood ethanol levels after hospital admission is probably due to the fact that acute ethanol poisoning responds very well to standard supportive care such as maintenance of free airways and administration of intravenous infusions.

Ethanol is rapidly and completely absorbed from the stomach, which has recently been shown to contain sufficient alcohol dehydrogenase activity to account for a first pass metabolism of ethanol [9]. The higher content of alcohol dehydrogenase (ADH) in the male gastric mucosa results in lower blood ethanol concentrations in men compared to women following ingestion of similar ethanol doses [10]. The volume of distribution of ethanol is 0.6–0.7 l/kg, with lower values in females. In ethanol poisoning, ethanol elimination is usually defined by zero order (non-linear) kinetics, since the main route of elimination, metabolism by the hepatic alcohol dehydrogenase system, becomes saturated. Renal, pulmonary and fecal excretion contribute very little to the elimination of ethanol. The elimination rate of ethanol ranges from 66–154 mg/kg/h with the highest values in drinkers. As a result, blood ethanol concentrations disappear at a rate between 0.06–0.40 g/l/h, with an average of approximately 0.15 g/l/h.

The inducible cytochrome P-450-mediated metabolism of ethanol (via CYP 2E1), or MEOS, normally contributes to a limited extent to the elimination of ethanol in non-drinkers. In drinkers, MEOS is often induced sufficiently so that it contributes more to the elimination of ethanol. As this system is not saturated at blood ethanol concentrations seen in acute poisonings, its relative contribution compared to the ADH-system (which is saturated) will be larger at higher ethanol concentrations. This is the most probable explanation for the first order (linear) or mixed elimination profile often seen at the start of the blood ethanol elimination curve in patients with high concentrations (>4–5 g/l).

Mechanisms of toxicity

Alcohol abuse, particularly chronic, is associated with effects on numerous organ systems, but in the scope of this chapter, the primary organ of concern is the central nervous system. The behavioral effects of ethanol include an initial stimulatory effect, but it is best known for its CNS depressant action (which is manifested during acute alcoholic intoxication). Ethanol produces effects directly on the cells of the CNS by several mechanisms and indirectly through induction of nutritional deficiencies (as in Wernicke's disease). As yet, there is no evidence for a specific ethanol receptor. Instead, the non-polar property of ethanol allows it to locate within the cell membrane, where it acts to increase the amount of lipid fluidity thereby disrupting membrane structural integrity.

In this way ethanol has actions similar to the mechanism of action of anesthetic agents. Ethanol is thought to act on specific membrane domains so that it interferes with membrane-associated proteins such as ion channels and receptors, leading to changes in ion transport or second messenger systems. In particular, ethanol enhances the inhibitory effects of GABA through effects at the GABA–chloride channel receptors.

Ethanol also inhibits production of the antidiuretic hormone in the pituitary gland resulting in an increased water diuresis. On the other hand, the increased serum osmolality caused by ethanol tends to increase the production of this hormone. The acute actions of ethanol on fluid and electrolyte homeostasis is not completely understood, but in practice this disturbance plays a minor role in acute ethanol intoxication in non-alcoholics. In contrast, the chronic alcohol abuser is usually mildly overhydrated with corresponding low serum electrolyte values for sodium, potassium and magnesium.

Clinical features

The main feature of ethanol intoxication that brings about hospitalization is CNS depression, which may result in a deep and prolonged coma. Hypotension and respiratory problems may also occur in patients not in deep coma, probably due to aspiration of vomit into the lungs, which may also cause pneumonia. Hypothermia can be caused by a combination of vasodilation and a loss of response to low ambient temperatures. The majority of patients do not develop other features though headache, dry mouth and a slight tremor may be present on recovery.

In normotensive patients, a mild metabolic acidosis (base deficit usually 4–5 mmol/l) may result from the increased redox ratio (NADH/NAD) caused by ethanol metabolism within the cells. In the more severe cases, a combined respiratory and metabolic acidosis may occur. Usually the latter component is more pronounced, because of lactate production during hypotension. Cardiac arrest may also occur, but the patient can often be resuscitated successfully [6]. Such cases can become critically ill and may also suffer from other complications such as adult respiratory distress syndrome, dissiminated intravascular coagulation, and acute renal or multiorgan failure.

Ethanol intoxication in children may be complicated by hypoglycemia, especially after an overnight fast. A typical example might be a child drinking from the half empty bottles on the morning after the parents' party. The same tendency to develop hypoglycemia, though less pronounced, may be seen in chronic alcohol abusers who suffer from malnutrition because ethanol consumption replaces the ordinary consumption of food-based calories. Malnutrition probably also contributes to the ketoacidosis ("alcoholic acidosis") in these patients. Typically this acidosis develops when the blood ethanol level is zero or close to zero. Some of these alcoholics may even have a metabolic acidosis with normal anion gap due to loss of bicarbonate via the gut ("alcoholic colitis").

Diagnosis

The most important diagnostic procedure in these cases, i.e. checking the patient for alcohol on the breath, is to rule out other causes for the coma. Among the most important other causes are head injury (epi- and subdural hematomas), hypoglycemia (children), and co-ingestion of drugs or toxic chemicals (e.g. methanol and ethylene glycol).

Ethanol is easily determined by gas chromatography which also allows the determination of methanol, isopropanol and acetone [11]. Automated clinical laboratory procedures involving enzyme-based methods are also easily used for detection of ethanol; interference by other alcohols or ketones may be a problem with these methods if co-ingestion occurs.

Management

If the patient is seen within one hour of ingesting a substantial quantity of ethanol, gastric lavage should be considered. Activated charcoal is of no value in pure ethanol intoxication, but since many patients have coingested other drugs which potentiate the toxic effects of ethanol, activated charcoal should be considered in most cases.

Symptomatic and supportive treatment should be given as needed, and intravenous dextrose should be administered to inebriated children, with regular monitoring of blood sugar. Dextrose should not be given to regular alcohol abusers unless thiamine has already been administered intravenously. Provided renal function is normal, alcohol abusers that are acutely intoxicated with ethanol can be treated with magnesium sulfate, 30–60 mmol $MgSO_4$ in isotonic glucose, over 12–24 hours to treat the hypomagnesemia usually present.

Hemodialysis effectively removes ethanol and should be considered in the severely poisoned patient with hypotension and depressed ventilation, especially if there is a documented co-ingestion. The blood ethanol concentration itself is not a good guide to the need for dialysis. For example, hemodialysis could be indicated in a critically ill patient poisoned with neuroleptics and ethanol if the blood ethanol concentration was above 3 g/l (65 mmol/l). Due to the potentiating effect of ethanol, the overall toxicity could be significantly reduced by removing ethanol from such a patient by dialysis. This would reduce the overall toxicity by decreasing ethanol levels to lower values that would not exacerbate the toxicity of neuroleptics (or other CNS depressants). On the other hand, hemodialysis would probably not be indicated if the blood ethanol concentration was 6 g/l (130 mmol/l) in a pure ethanol ingestion and the patient had no other complications apart from coma. Dialysis should not be advocated if the patient has to be transferred a considerable distance away as supportive therapy cannot be carried out properly.

ISOPROPYL ALCOHOL

Isopropyl alcohol (isopropanol, 2-propanol, "rubbing alcohol") is a colourless, volatile liquid with a characteristic odor and a slightly bitter taste. It is widely used as a solvent, as a sterilizing agent and as rubbing alcohol. It is also found in various cosmetic products and window-cleaning solutions.

Epidemiology

Isopropyl alcohol plays an important role as the poor man's substitute for alcohol, probably because many users know that this compound is not as dangerous as methanol or ethylene glycol. Isopropanol is therefore one of the most common causes of acute intoxication, although those admitted to the hospital present only a small fraction of the total number of intoxications (many cases are "self-treated" through supportive care and sleep).

Toxicology and toxicokinetics

The kinetics or effects of isopropyl alcohol have not been well characterized in humans. The lethal dose is quite variable, given as 1–4 ml/kg. An often repeated claim which virtually lacks documentation, is that isopropyl alcohol is twice as toxic as ethyl alcohol. The reason for this greater toxicity may be that this alcohol is more lipid soluble and thus may produce a greater CNS depression than do molar equivalent amounts of ethyl alcohol. In our experience isopropyl alcohol intoxication, on a practical level, does not appear to be twice as dangerous as ethyl alcohol poisoning.

Blood isopropanol levels in the range of 2–4 g/l (34–68 mmol/l) are often seen in our department with few complications other than slight coma and respiratory depression. Others have reported survival with blood levels as high as 5.6 g/l (95 mmol/l) although hemodialysis had been used [12]. It is, however, difficult to evaluate the toxicity of this compound. Many cases involve chronic alcoholics and the lethality might result from complications of alcoholism as well as isopropyl alcohol toxicity.

Isopropyl alcohol is rapidly absorbed following oral intake and may even be absorbed following cutaneous application. Like the other small alcohols, its apparent volume of distribution is close to 0.7 l/kg suggesting total body water distribution. The elimination profile appears to follow linear first order kinetics with a serum half-life ranging from 2.5–4 h [13,14], although values in the 6–8 h range have also been reported [14,15]. Coingestion of other alcohols such as ethanol would produce competition for the enzyme alcohol dehydrogenase, which is the major metabolizing enzyme for isopropyl alcohol. This may explain the slower elimination reported in some cases [14].

The major metabolite of isopropyl alcohol is acetone (>80%). Acetone levels upon initial contact are usually much higher than the initial alcohol level, probably because of its slower elimination compared to isopropanol [15]. A small amount of isopropyl alcohol is excreted unchanged in the urine.

Mechanism of toxicity

The mechanism of isopropyl alcohol toxicity is probably much like that of ethanol. Being more lipid soluble, its CNS depressing effects are more pronounced.

Clinical features

The feeling of drunkenness is much the same for ethanol as for isopropanol, though the latter may "hit you a little harder". Another unpleasant aspect of isopropanol is the occurrence of headache which starts even during the intoxication, i.e. before the "hangover" period after intoxication. This may, however, be due to the presence of contaminants in the technical spirits that are usually sold in Scandinavia. One problem is gastritis which almost always leads to a slight bleeding (and pain) during gastric decontamination. It is unclear whether this is due to the contaminants from the ingested liquid, the isopropyl alcohol itself or that these patients are often chronic alcoholics. Contaminants probably explain gastritis, abdominal pain and slight hematemesis to some extent, but abdominal pain also occurs in patients who have drunk pure isopropyl alcohol only.

The typical patient used to present with various degrees of CNS depression and slightly depressed respiration and slight hypothermia. Aspiration pneumonia may be present, especially if he was found lying on the back or out in the cold. Hypoglycemia may be present in the very young and the severe alcoholic.

According to the literature review by Lacouture et al. [12], the combination of coma and hypotension was associated with a 45% mortality from isopropanol. Although our experience suggests that this number is too high, hypotension is associated with a more severe clinical course after isopropanol.

Diagnosis

The clinical diagnosis of isopropyl alcohol can be based on the CNS depression and the presence of acetone on the breath, but the latter may often appear as a general foul breath without the distinct acetone scent. Urine ketostix, sensitive only for acetoacetate, may be positive, but this test lacks specificity and is of no practical value.

Both isopropyl alcohol (1 g/l = 17 mmol/l, which generates 18 mosm/kg H_2O) and acetone increase the osmolal gap. The anion gap is usually normal but may be slightly increased due to ketosis (or lactic acidosis) in the alcoholic and lactic acidosis in the hypotensive patient. Isopropyl alcohol is best determined by standard gas chromatographic methods in which ethanol, methanol and acetone are determined as well.

Management

If the patient is seen within 1–2 hours after ingestion, decontamination by gastic lavage should be performed; activated charcoal overwhelmed by the

large molar amounts of alcohol is of no value. Due to the frequent irritation of the gastric mucosa in these patients, gastric lavage should be performed with special care; when blood appears in the aspirate, ice-cold water lavage should be performed. At the end of the procedure, the last dose of ice-cold water should be kept in the stomach for a minute before removal.

Symptomatic treatment should follow the established principles of intensive supportive care. Because many patients are not dehydrated and some have a general "hypoelectrolyte syndrome", IV fluids should not be given to hypotensive patients before vasopressors are used. Mechanical ventilation should be liberally employed if respiratory depression is accompanied by pneumonia.

Hemodialysis will effectively remove isopropyl alcohol with approximately the same efficacy as for ethylene glycol. The dialysance is about 130 ml/min for a 1.6 m^2 dialyzer at a blood flow of 200 ml/min. Guidelines for dialysis are difficult to promulgate because few studies have documented the blood levels of isopropyl alcohol at which toxicity is to be expected. Long transport to dialysing units should also be avoided (unlike in methanol and ethylene glycol poisonings) because the critical period is the early course of the intoxication, i.e. when patients are better off in a hospital intensive care unit. Nevertheless, hemodialysis should be contemplated at blood isopropanol levels about 3–4 g/l (50–70 mmol/l), especially if clinical criteria such as coma or sustained hypotension, are present. Because of numerous clinical complications in chronic alcoholics, hemodialysis may even be considered at lower blood levels.

METHANOL

Methanol (methyl alcohol, wood-alcohol) is a colourless, volatile and easily flammable liquid. It has a weak, peculiar smell which makes it difficult to recognize in the mixed liquids involved in many poisonings. Methanol is widely used industrially as a solvent and in the production of formaldehyde and methylated compounds. It is also widely available to the general public since it is found in several automobile antifreeze preparations and in various solvent formulations. The future introduction of methanol as an alternative fuel will expose far more people to this substance and result in more frequent poisonings. Unfortunately, methanol currently plays the role of a low-cost substitute for ethanol, particularly in countries with high taxes or other strict restrictions on ethanol use and sale.

Epidemiology

Methanol poisoning is actually rare, but when it occurs, many people are often involved simultaneously, hence the special place of methanol poisonings in clinical toxicology. Examples of mass poisonings include the Atlanta outbreak, which involved 323 people, of whom 41 died [16], and the Kristiansand outbreak with 70 people involved and 3 deaths [11,17]. Due to concomitant

ethanol consumption (see below), and more importantly the effective triage and treatment, no deaths occurred after the diagnosis of methanol poisoning was achieved in later outbreaks. Thus, early diagnosis, triage and effective treatment are essential to reduce mortality and morbidity.

Toxicology and toxicokinetics

The lethal dose of methanol is reported to be from 30–240 ml. The most probable explanation for this almost ten-fold variation is the contamination of the consumed liquid with ethanol or later ethanol consumption, as ethanol has a protective effect. Other explanations include notoriously poor histories reported in some of these cases and the differing folate status of patients. It is reasonable to regard 1 g/kg (1 g = 1.2 ml) as the minimum lethal dose in humans [18]. The minimum dose causing permanent visual defects is not known with certainty.

Methanol is rapidly and probably completely absorbed from the gastrointestinal tract (as well as via the skin and lungs). The volume of distribution has been calculated to be 0.7 l/kg in two male patients [11]. In a patient with a missed diagnosis for several hours so that pre-treatment blood samples were not available, a zero-order elimination pattern was clearly demonstrated (blood methanol concentration range: 1.4–0.5 g/l) at a rate of 0.085 g/l/h [19]. The K_m value for the rapidly saturable elimination could not be established, but was apparently lower than that of ethanol.

Mechanism of toxicity

Methanol itself has a low toxicity and the toxic effects have been described as "disappointing" by experienced drinkers. Patients with blood methanol concentrations of 3–6 g/l (66–132 mmol/l) showed no signs of being intoxicated [11]. The lack of correlation with blood levels and the typical latency before the development of symptoms suggested that toxic effects must be due to metabolites. Studies on the mechanism of methanol toxicity have been hampered by the fact that non-primates (of normal folate status) do not develop toxicity when exposed to methanol [20]. Studies in primates, however, have demonstrated that methanol toxicity is closely related to metabolites [20,21].

Methanol is metabolized in the liver by alcohol dehydrogenase to formaldehyde and further to formic acid which accumulates in primates due to their limited folate pool. Due to the larger liver folate pool in non-primates, formate does not accumulate and toxicity does not develop. If rats are rendered folate deficient, they become acidotic to a similar degree as do primates [22,23]. Formate has also been shown to account for the ocular toxicity of methanol in primates [21].

A pure formic acid acidosis has been found in the early stages of poisoning in non-alcoholics [17], but lactate probably contributes to acidosis in the later stages [24,25]. These findings may be explained as follows: in the early stage

of methanol poisoning, the toxic effects are due to increasing metabolic acidosis caused by the accumulation of formic acid. Later on, the increased concentrations of formate inhibit the respiratory chain within the cells resulting in lactate production. Acidosis is increased which in turn exacerbates formate toxicity as more formate is protonated and penetrates the blood–brain barrier. Thus a vicious circle or circulus hypoxicus' is initiated [25].

What remains to be explained is the reason why the ocular system and the basal ganglia, particularly the putamen, are the primary neurological targets of methanol toxicity and why chronic alcoholics who regularly drink methylated spirit (namely ethanol with 5% methanol) are more resistant to methanol toxicity [26].

Clinical features

Usually, there is a latent period of 12 to 24 hours between methanol ingestion and the development of symptoms even though shorter intervals have been reported following ingestion of very large quantities. The latency represents the time needed for sufficient amounts of formic acid to accumulate. Since ethanol inhibits methanol metabolism, concomitant ethanol intake may considerably lengthen the latent period and even abolish toxicity completely. A delay in the development of clinical features of approximately 90 hours was seen in two patients who continued to drink ethanol for two days following methanol consumption [11].

The first symptoms of methanol poisoning are non-specific and include weakness, anorexia, headache and nausea with increasing dyspnoea (hyperventilation) as metabolic acidosis develops. Visual disturbances (e.g. blurred vision) may appear first or together with the symptoms described above. Progressing dyspnoea is most commonly associated. Usually symptoms precede the objective signs of ocular toxicity including dilated pupils, which become partially or non-reactive to light, and optic disc hyperemia with blurring of disc margins. A few patients may present with acute pancreatitis.

If treatment is not initiated at this early stage of poisoning and hence more methanol is metabolized, the patient develops pronounced CNS depression with coma, followed by respiratory and circulatory failure as terminal events. Deterioration may occur within a few hours to days. In our experience, cyanosis due to methemoglobinemia seldom occurs, possibly because of an interaction between formate and the ferric part of hemoglobin.

Toxic effects on the putamen do not result in detectable symptoms at the acute stage, but at a later stage as they are often concealed by the pronounced central nervous depression. Survivors of the initial insult can present with permanent neurological deficits [27].

Diagnosis

Clinical diagnosis of methanol intoxication is difficult without a history of ingestion. Clinical features, such as hyperventilation, blurred vision, impaired

consciousness, sluggish pupils and fundoscopic changes develop relatively late in the course of poisoning. For specific analysis, methanol is best detected in blood by standard gas chromatography, and ethanol, isopropanol and acetone are determined as well [11].

If a specific analytical method for methanol is not available, the anion and osmolal gaps should be calculated as discussed previously. Elevation of these gaps is a strong indication of methanol (or ethylene glycol) poisoning when the common pitfalls in interpretation of these gaps are taken into account.

Management

The treatment should follow the established principles of intensive care when needed. If the patient is seen within a few hours, gastric lavage should be performed. Activated charcoal is of no value except if ingestion of other pharmaceuticals is suspected. The specific treatment of methanol poisoning includes administration of sodium bicarbonate to combat the metabolic acidosis, ethanol (or 4-methylpyrazole) to inhibit methanol metabolism to formate, and hemodialysis to increase the removal of methanol and formate from the body.

The metabolic acidosis should be aggressively treated by infusion of sodium bicarbonate. One should aim at a full correction of acidosis and as much as 400–600 mmol bicarbonate may be required during the first hours. If ethanol or 4-methylpyrazole is not available, aggressive bicarbonate treatment must be continued to counteract the continuous production of organic acids and to increase the dissociation of formic acid to limit its access to the central nervous system.

Alkali treatment must be associated with ethanol administration; otherwise the acidosis may become bicarbonate-resistant since formic acid is continuously produced. Experience has shown that a therapeutic blood ethanol concentration of 22 mmol/l (1 g/l) is adequate. Ethanol therapy should be continued until the methanol concentration drops below 6 mmol/l provided there is a normal acid/base status and no (visual) complications. However, it must be emphasized that the therapeutic blood ethanol concentration depends on the concomitant blood methanol (or ethylene glycol) concentration as there is a stoichiometric competition for alcohol dehydrogenase. Therefore, ethanol concentrations lower than 22 mmol/l may be sufficient at low blood methanol concentrations.

A blood ethanol level of 22 mmol/l (1 g/l) may be approximated by giving a bolus dose of 0.6 mg/kg of absolute ethanol, followed by 66 to 154 mg/kg/h intravenously (or orally) with a higher maintenance dose for drinkers. Alternatively, 60 ml (50 g) absolute ethanol (for a 75-kg individual) should be added to 500 ml isotonic glucose or saline, and given intravenously over 15 min, followed by the same mixture at a rate of 100 ml/h (12 ml ethanol/h) with adjustments as needed for previous ethanol-consuming habits. Monitoring blood ethanol levels is important because of the difficulty in maintaining consistent blood levels (owing to interindividual variations in ethanol metabolism and the peculiar non-linear elimination kinetics of ethanol). It is especially important

to monitor blood ethanol levels during hemodialysis since ethanol is readily dialyzed. As a general rule, the maintenance dose of ethanol should be doubled during hemodialysis. Because depressive levels of ethanol are recommended to be attained (1 g/l), ethanol administration may increase CNS depression in later stages of methanol poisoning. Blood methanol concentrations are then usually low, so that bolus ethanol may be given at a slower rate (over 20–30 min). The role of 4-methylpyrazole (4-MP) as an antidote will be discussed later.

Hemodialysis to remove methanol and formate is indicated for: (1) any degree of visual impairment, provided that methanol, formate or metabolic acidosis is still present; (2) severe metabolic acidosis (base deficit >15–20 mmol/l), (3) Blood methanol levels above 20 mmol/l (60 mg/dl); (4) Methanol ingestion of more than 40 ml (adults).

Of these, the first is an absolute indication for dialysis, whereas the last two could be questioned. If patients in these categories are seen early, hemodialysis may not be necessary as proper ethanol treatment has been shown to prevent elevation of plasma formate levels and thereby toxicity [28]. Hemodialysis, preferably using a bicarbonate-based dialysate, should be continued until the blood methanol level is below 10 mmol/l (30 mg/dl) and the acidosis corrected. If methanol assays are not available, hemodialysis should be continued for at least 8 hours. Peritoneal dialysis can also remove methanol, but not as effectively.

Although of no proven efficacy in humans, folic acid or folinic acid (leucovorin) may also be of value in increasing formate metabolism by providing additional cofactors. Studies in primates have shown that folates increase formate metabolism and decrease its accumulation after methanol [29]. 50–70 mg (adult dose) folinic acid should probably be given intravenously every 4 hours for 24 hours [30]. There is, however, no experimental basis for selecting these doses, and smaller amounts may be effective. This treatment should be given as soon as possible and particularly when ocular symptoms are present. However, it is not as high priority as alkali, ethanol and hemodialysis treatment and these should never be delayed to initiate folate therapy.

In situations involving many patients, it is not always possible to follow sophisticated treatment protocols. Treatment has to be simplified accordingly and emphasis put on proper triage of admitted patients. The Kristiansand outbreak showed that patients with only few symptoms, despite very high methanol concentrations, could easily be transported by plane or helicopter to other dialysis units, provided that they were treated with ethanol during transport.

Complications

Patients, upon receiving aggressive treatment, have been shown to recover from an initial loss of vision. However, there is usually little improvement of impaired visual acuity when progressing beyond the acute stage. The patient should be repeatedly evaluated by an ophthalmologist.

Better diagnosis and treatment might ironically lead to an increasing num-

ber of survivors with a Parkinson-like syndrome [27,31,32]. This syndrome is probably the clinical correlate of bilateral symmetrical lesions in the putamen and hemorrhages in subcortical white matter [27,32]. This complication has previously been described post-mortem, when diagnostic and therapeutic measures were less sophisticated [33].

ETHYLENE GLYCOL

Ethylene glycol is a colourless, nearly non-volatile liquid with an aromatic odor which can be recognized from the breath of some victims. It is widely used as antifreeze in internal combustion engines, but also as a solvent and for various manufacturing processes.

Epidemiology

Although few comparable epidemiological data exist, ethylene glycol poisoning appears to be more frequent than methanol intoxication [34]. Few instances of mass poisoning have occurred, but several patients have occasionally been seriously poisoned at the same party. Announcement of cases in the media has also led to multiple "copycat" cases (Persson H, personal communication). Besides being substituted for ethanol, ethylene glycol has been used in planned suicidal attempts. In the prospective Oslo 1980 study with 1212 acute poisonings in adults, only five were due to ethylene glycol and two due to methanol [5]. In 1979, the numbers were 5 and 20 respectively in a "methanol outbreak".

Toxicology and toxicokinetics

The lethal dose of ethylene glycol is not well established, but 100 ml is the most frequent estimate. A value of 1–2 ml/kg seems reasonable.

Ethylene glycol is rapidly and probably completely absorbed following oral administration. The volume of distribution is usually considered to be 0.7 l/kg based on studies in two male patients [35], though values of 0.54 l/kg [36] and 0.83 l/kg [37] have also been reported in males.

Ethylene glycol elimination kinetics have not been determined completely. There is evidence for a saturable elimination with linear (first order) elimination for plasma concentrations below 40 mmol/l (2.5 g/l) with a half-life of about 8 hours in a patient with ensuing renal failure [36]. Animal data suggest a more rapid elimination [38].

In one male patient, the volume of distribution of the metabolite glycolate was calculated to be 0.6 l/kg with an estimated intrinsic half-life of 7 hours for the concentration range studied [36].

Mechanisms of toxicity

Like methanol, the toxicity of ethylene glycol is mediated through its meta-

bolites. However, unlike methanol, ethylene glycol causes a significant CNS depression and inebriation in a similar manner to ethanol.

Historically, the formation of oxalate has been considered the main reason for ethylene glycol toxicity, probably based on the visualization of oxalate-like crystals in the urine and the development of the acute renal failure. Later, Parry and Wallach [39] suggested that the aldehydes formed — mainly glycolaldehyde — were responsible for the toxic syndrome. Such aldehydes are known to inhibit oxidative phosphorylation, glucose metabolism, protein synthesis, DNA replication and RNA synthesis, and may also oxidize intracellular SH-groups.

As judged from experimental studies, there appear to be no major differences in the way rodents and humans responds to ethylene glycol, based on the fact that both experience acidosis and acute renal failure. Therefore the relative toxicities of ethylene glycol metabolites (glyoxylate > glycolaldehyde > glycolate) established in rodents may also have validity in humans [40]. However, in experimental studies with ethylene glycol-intoxicated rats, dogs or monkeys, neither glycolaldehyde or glyoxylate were detected using GC-MS techniques [41–43]. In addition, in six patients poisoned with ethylene glycol, glyoxylate levels were <0.2 mmol/l and glycolate levels were in the range of 17–29 mmol/l [44]. Of the relevant metabolites, only glycolic acid thus appears to be present in significant amounts to produce toxicity.

The toxicity of ethylene glycol is therefore a combination of severe metabolic acidosis caused by glycolic acid and the deposition of calcium oxalate crystals, which results in impaired organ function. Unlike the significant role defined for the formate ion in methanol poisoning, the anion glycolate per se has not yet been linked with toxicity (other than with acidosis). Hypocalcemia and the resulting tetany/seizures are unlikely to play a major role in ethylene glycol poisonings.

Clinical features

Ethylene glycol poisonings are characterized by initial CNS depression with inebriation progressing to coma. Following a short latent period of 4–12 hours, the symptoms due to metabolite accumulation start to appear. The increasing accumulation of glycolic acid leads to severe metabolic acidosis and increasing hyperventilation. In contrast to methanol poisoning, these patients usually are in coma when hyperventilation is pronounced so there is no subjective feeling of dyspnoea. For unknown reasons, elevated blood pressure and tachycardia are usually prominent features.

At this stage (4–18 hours post-ingestion), urine output is usually good. If proper treatment is started at this stage, full recovery often occurs even though the patient may suffer from complications of calcium oxalate precipitation such as acute kidney failure and hypocalcemic-induced tetanic contractions. The prognosis of the renal failure is generally good, although the plasma creatinine may not return to normal for months.

Without adequate treatment, the patient will deteriorate rapidly with development of severe CNS depression (cerebral edema), convulsions, oliguric renal failure and respiratory problems. Pulmonary infiltration may be observed radiologically, although these changes appear to be non-infective in origin. Since precipitation of calcium oxalate crystals also occurs in the lungs, one could postulate that these changes may be an inflammatory reaction related to this precipitation. Although pulmonary edema has been suggested to occur in ethylene glycol poisoning, this is an unsubstantiated diagnosis, despite a similar appearance. In severe cases, acute respiratory distress syndrome may develop.

Even patients admitted in extremis may survive on the first days provided adequate treatment is given. Such patients should undergo a CT head scan to evaluate the degree of brain damage. Many of these patients will develop (large) cerebral infarcts or cerebral edema resulting in brain death.

Ocular manifestations and methemoglobinemia have been reported [45,46]. However, no analytical investigations were performed to rule out methanol contamination of the liquid ingested. We have seen one ethylene glycol intoxicated patient with visual dyspraxia as a result of cerebral infarcts. No objective ocular complications could be observed in this or many other patients.

Diagnosis

Ethylene glycol in biological fluids can be determined by gas chromatography [47] but these methods have previously been more difficult to perform than those for methanol, ethanol and isopropanol. Aarstad et al. [48] have recently developed a rapid and accurate method for the detection of ethylene glycol in serum and urine. This new method will hopefully improve the diagnosing of ethylene glycol poisoning.

If specific GC analysis is not available, the use of the anion and osmolal gaps may also point to the diagnosis, as discussed previously in this chapter. Theoretically, the sensitivity of the osmolal gap should be low at ethylene glycol concentrations below 0.5 g/l (8 mmol/l), but for unknown reasons, the osmolal gap tends to be higher than expected from the molar contribution of ethylene glycol at such low levels.

Urine microscopy can reveal envelope-shaped or needle-shaped oxalate crystals. Findings may be delayed and a negative microscopy should therefore be repeated [36]. The crystalluria is massive and easy to detect even by an unexperienced microscopist. In addition, there are erythrocytes, leucocytes, and different casts in the urine sediment.

Management

Treatment should follow the well established principles of supportive care. If the patient is seen within the first two hours, gastric lavage should be performed whereas activated charcoal is of no value.

Metabolic acidosis should be aggressively treated by sodium bicarbonate infusion as in methanol poisoning. Since ethylene glycol is metabolized faster than methanol, acidosis may develop more rapidly in situations where ethanol (or 4-methylpyrazole) is not given, resulting in a bicarbonate-resistant' metabolic acidosis [49]. The rapid correction of acidosis in these patients may induce tetanic signs, especially when hypocalcemia is already present.

Ethanol (or 4-methylpyrazole) is given to inhibit ethylene glycol metabolism. The dose regimen should be the same as in methanol poisoning. Although alcohol dehydrogenase affinity for ethylene glycol is lower than for methanol [50], this makes little practical difference and ethanol treatment should be continued until ethylene glycol has been fully eliminated from the body. Several studies have indicated that ethanol can significantly inhibit ethylene glycol elimination [37,51]. An apparent half-life of ethylene glycol elimination of 17 hours during ethanol therapy was demonstrated by Peterson et al. [37] in a patient without kidney failure; this finding can be compared to a half-life of 4–8 hours without ethanol administration [36]. A similar half-life of 12 hours was observed by Baud et al. [52] using 4-MP instead of ethanol in a patient without kidney failure; the elimination of ethylene glycol in these metabolically limited situations is primarily due to its renal excretion.

The dialysance of ethylene glycol has been well documented [35,37]. As should be expected from its higher molecular weight than that of methanol (62 vs. 32 D), ethylene glycol is less dialysable than methanol (160 vs. 130 ml/min, using a 1.6 m^2 dialyzer at blood flow of 200 ml/min). The dialysance of the major toxic metabolite glycolate has also been documented [44]. Since ethylene glycol has no significant pulmonary elimination, hemodialysis is the major route of glycol removal from the body when ethanol is administered and renal failure is present. Furthermore, hemodialysis offers the additional possibility of correcting metabolic and electrolyte disturbances in these patients.

Once initiated, hemodialysis should be continued until ethylene glycol can no longer be detected in the blood and there are no acid-base disturbances. If blood concentrations of ethylene glycol are not available, hemodialysis should be continued for at least 8 hours, or longer if the acidosis is not corrected; persistent acidosis indicates that too little ethanol has been given during hemodialysis. If hemodialysis is not available, peritoneal dialysis can also remove ethylene glycol [53], though less efficiently. Hemoperfusion is not effective.

If the patient is seen at an early stage, i.e. before severe metabolic acidosis and renal impairment have developed, hemodialysis may not be necessary. Hewlett et al. [51] successfully treated a child admitted at such an early stage with ethanol and bicarbonate alone. Recently Baud et al. [52,54] and Jaeger (personal communication, 1990) treated several patients with 4-methylpyrazole and bicarbonate alone. Under such circumstances, further metabolism of ethylene glycol to its toxic metabolites is inhibited and the glycol is excreted through the kidneys with a plasma half-life of approximately 2–3 times the normal value. The onset of acute renal failure may require repeated hemodialysis, hemofiltration or peritoneal dialysis.

Tetany and seizures should be treated with calcium gluconate intravenously as hypocalcemia is an important cause of these complications. Calcium *should not be given* to treat hypocalcemia per se as this may increase precipitation of calcium oxalate crystals in the tissues. If calcium gluconate is not effective, convulsions should be treated conventionally.

DIETHYLENE GLYCOL

There is too little information about diethylene glycol poisonings in humans to allow for any absolute recommendations regarding the treatment of acute poisonings.

The clinical course and the pathological features have, however, been described in several reports of which the sulfanilamide "Massengil disaster" is probably the best known [55]. Here diethylene glycol (73%) was used as a vehicle for the preparation of 10% sulfanilamide to treat infections. A total of 105 deaths due to renal failure were related to this sulfonamide formulation. No oxalate crystals were reported in the kidneys or other organs of these victims, but the variation in appearance of oxalate crystals was probably not known for most clinicians before 1980 [56]. Except for the lack of oxalate crystals, the pathological findings in the various organs of these victims were much the same as those found in ethylene glycol-poisoned victims.

Experimental studies in rats exposed to diethylene glycol clearly showed similarities with rats experiencing ethylene glycol toxicity [57,58]. The animals developed metabolic acidosis as in ethylene glycol toxicity [51] and mortality was reduced if animals were treated with bicarbonate or ethanol. The administration of ethanol reduced mortality to nil and prevented acidosis. Untreated animals developed acute tubular necrosis with renal oxalate crystals deposits. A rat study comparing some aspects of ethylene glycol and diethylene glycol toxicity showed that blood and kidney oxalate concentrations were higher when ethylene glycol was given [59]. Based on these data it is be reasonable to conclude that the toxicity and treatment of ethylene glycol and diethylene glycol toxicity are similar, at least in rats (a reasonably good animal model).

In humans exposed to diethylene glycol, the presence of acidosis has been questioned, but this may be due to the fact that more emphasis has been given on pathological findings in these fatal cases than on clinical and metabolic features [60]. There is at least one clinical report of metabolic acidosis in children [61]. Topical application of silver sulfadiazine contaminated with diethylene glycol to patients with burns resulted in an increased anion gap metabolic acidosis and acute renal failure. All five patients died despite supportive treatment and bicarbonate replacement [62]. Autopsy was performed in one patient with no evidence of oxalate crystals.

As is evident from the discussion above, diethylene glycol poisonings should be treated as recommended for ethylene glycol poisonings. Until more data are available, ethanol, not 4-methylpyrazole, should be used in order to prevent the assumed formation of toxic metabolites by alcohol dehydrogenase in the liver.

POLYETHYLENE GLYCOL

The polyethylene glycols are liquids at low molecular weights, solid when the molecular weight is above 1000. Toxicity decreases with increasing molecular weight, probably due to poor absorption of the solid forms. In general, the toxicity is low. This group is used as solvents for different purposes.

Little is known about the clinical features of poisonings. The reported CNS depression, metabolic acidosis, and renal failure point to some similarities with ethylene glycol poisoning [63,64].

The standard measures of gastric decontamination (lavage/emetics) are probably the mainstay of therapy in these rare poisonings. The efficacy of hemodialysis is hampered by the relatively high molecular weight. If severe metabolic acidosis develops, ethanol treatment may be applied as in ethylene glycol poisoning but this treatment has not been documented.

PROPYLENE GLYCOL

The use of propylene glycol (1,2-propanediol) in various cosmetics probably has little toxicological significance. Its use as a solvent for intravenous drug formulations has demonstrated that this compound is not completely inert from a toxicological point of view. Renal failure may result in retention of the glycol since about 50% is excreted in unchanged form by the kidneys, whereas the rest is metabolized mainly to lactate, acetate and pyruvate [65]. In such situations, propanediol could accumulate to significant levels and produce CNS depression. Metabolic acidosis may be pronounced due to metabolism to lactate (up to 24 mmol/l) [66]. The elimination half-life is about 19 hours [67]. In two children, CNS depression and seizures were observed following propylene glycol intoxication [68,69]. S-propylene glycol levels of 760 mg/dl did not cause any central nervous depression [70].

Treatment is supportive following gastric decontamination. The effect of activated charcoal has not been documented. Note that this glycol (molecular weight 76) may also increase the osmolal gap. If lactic acid acidosis develops, this rare poisoning may thus raise both the osmolal and the anion gaps.

ALKYL ETHERS OF ETHYLENE GLYCOL (CELLOSOLVES)

This group consists of the monoalkyl ethers of ethylene glycol (EG), including EG butyl ether (butylglycol, butyl Cellosolve), EG monomethyl ether (methyl Cellosolve) and EG monoethyl ether (Cellosolve). These compounds are mainly used as solvents and cleaning compounds. Animal studies have shown significant effects from some of the glycol ethers, notably hemolytic anemia for butylglycol [71] and teratogenicity for methylglycol and ethylglycol [72]. The potential for human toxicity has not yet been established. Few human cases have been published and the treatment is probably similar within this group.

Butylglycol poisoning has been reported following the suicidal ingestion of a

window-cleaning agent containing butylglycol (ethylene glycol monobutyl ether) and ethanol [73]. Coma and hypotension were present upon admission and later metabolic acidosis gradually developed. The metabolic acidosis was due to the butylglycol metabolite, butoxy acetic acid, and to lactate. No increase in urine oxalate content was observed. The ingested dose of butylglycol was about 25–30 g giving a blood level of 0.43 g/l upon admission. The patient was treated with forced diuresis, bicarbonate and hemodialysis. There was an indication of ethanol inhibition of butylglycol metabolism and of an effect of hemodialysis in this patient. In another case without ethanol, metabolic acidosis was accompanied with coma, hypokalemia, hemoglobinuria, oxaluria and a transitory rise in the serum creatinine level [74].

Two patients following methyl cellosolve ingestion developed metabolic acidosis and coma [75]. The patient with the most severe metabolic acidosis developed slight acute renal failure and urine oxalate crystals were observed. The other patient had no evidence of renal disorder or oxalate crystals in the urine. They both had an uneventful recovery following treatment with bicarbonate and ethanol.

Based on these case reports and overall theoretical considerations, it would be reasonable to treat these poisonings like those with ethylene glycol poisoning. Until more data are available, ethanol, not 4-methylpyrazole, should be used in order to prevent an assumed formation of toxic metabolites by the alcohol dehydrogenase in the liver.

BENZYL ALCOHOL

This aromatic alcohol is still used as a bacteriostatic preservative in heparin solutions used during hemodialysis. This may lead to a slight accumulation of unknown significance. Benzyl alcohol was previously used in solutions for premature neonates. Owing to their metabolically immature liver, the biotransformation to benzoic and hippuric acid was low leading to toxicity and death — the so-called "gasping syndrome" [76].

For practical purposes, toxicity appears to be low and treatment is symptomatic. Benzyl alcohol is dialysable, but the effect of dialysis has not been evaluated in these poisonings.

There are no reports on the clinical course of these rare poisonings but the major effect would probably be central nervous depression. The multiorgan failure described in the "gasping syndrome" is unlikely to be observed in acute overdose with a metabolically intact liver.

4-METHYLPYRAZOLE — PRESENT STATUS

The possible replacement of ethanol by 4-methylpyrazole (4-MP) as antidotal therapy in methanol and ethylene glycol poisonings has been discussed for years [20,77]. The possible advantages of 4-MP include a much slower elimination, a stronger inhibition on alcohol dehydrogenase and a presumed

lesser degree of adverse effects. It is well known that maintaining therapeutic blood ethanol levels is difficult due to unpredictable elimination rate, especially during hemodialysis. 4-MP administration might offer the additional advantage of being more easily administered and controlled.

Following preclinical studies, clinical phase I studies have been carried out in healthy volunteers [78,79]. In summary, findings were that 4-MP appeared to be a safe and promising new drug for the treatment of methanol and ethylene glycol poisonings so that phase II studies are now being planned in the U.S. There was an indication of slight liver affection in 40% of the healthy subjects, but the minor increase in transaminases was transient [79]. The elimination of 4-MP did not follow the ordinary Michaelis–Menton kinetics and can best be explained by a two-enzyme elimination model [78]. Unpublished data using an experimental pig model indicate removal of 4-MP by hemodialysis, but at a much slower rate than ethanol. An overall conclusion would be that the dosing of 4-MP to poisoned patients would be easier to perform than that of ethanol.

The initial clinical use of 4-MP in ethylene glycol poisoned patients in France paralleled our own studies. It has been shown to be very effective in several cases in which an effective inhibition of ethylene glycol metabolism was achieved [52,54]. No 4-MP levels were, however, determined in these studies and the exact dosage of 4-MP has yet to be determined. A dose regimen for 4-MP in methanol or ethylene glycol poisonings cannot yet be suggested. However, if 4-MP is used according to the previously suggested doses [52,79], blood samples should be collected for 4-MP determinations as well.

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Human Toxicology. J. Descotes (Ed.)

F. Testud and J. Descotes

25. Aldehydes, esters, ketones, ethers and amines

ALDEHYDES

Aldehydes are highly reactive chemicals with one or more [–CH=O] groups. Toxicity decreases with the number of carbon atoms and also depends on the presence or absence of unsaturated links: for a given number of carbon atoms, the unsaturated aldehyde is more toxic than the saturated homolog. In most cases of low to moderate exposure, no systemic toxicity is involved because aldehydes covalently bind with proteins of superficial tissues and systemic diffusion is low.

Formaldehyde

Formaldehyde is a flammable colourless but suffocating gas, known since 1859, and now industrially prepared from methanol by oxidation with air. Formalin is an aqueous solution of 30 to 50% formaldehyde (37% in the USA) with 10 to 15% methanol added to prevent polymerization. Half of the world-wide production is used in the manufacture of urea–formaldehyde, phenol–formaldehyde and melamine–formaldehyde resins for bonding of pressed wood-products [1]. Urea–formaldehyde foam insulation is another important use and source of non-occupational exposure in indoor air. Other applications include textile and paper industries, rubber manufacturing and tanning. Formaldehyde is a major biocide used as medical sterilant (usually 6–10%) and preservative in cosmetics and household cleaning agents.

Formaldehyde occurs naturally in food and most animal species, including humans. It is also an environmental pollutant, present in automobile exhaust, cigarette smoke, photochemical smog, and thermodegradation products of many natural or synthetic materials.

The toxicity of formaldehyde in humans has been the matter of several recent reviews [1–4]. It is a strong irritant to the eyes, skin and upper respiratory tract. Burns and acute respiratory distress following heavy exposure have been reported. Formalin ingestion results in severe corrosive injury, which

predominates in the stomach [5,6]. Fatalities have occurred from multivisceral failure: acidosis, seizures, hemolysis, rhabdomyolysis, circulatory collapse, renal and hepatic damage. Therefore, conventional management of large and recent ingestions may include gastric aspiration in view of systemic toxicity. N-acetylcysteine infusion has been proposed. Burkhart et al. [6] reported a fatal suicidal ingestion of 120 ml of formalin with formic acid (formate) and methanol levels rising until the patient's death 13 hours later, possibly a result of delayed absorption by "fixing" the stomach.

Contact urticaria, ocular, nose and throat irritation occur with levels from 0.1–2 ppm and above, with large individual variations. Significantly more respiratory symptoms were observed among exposed workers at a paper mill [7] where mean exposure levels (0.02 ppm) were well below the Threshold Limit Value (TLV) recommended by the American Conference of Government Industrial Hygienists (ACGIH) in 1991 (0.3 ppm). Asthmatics and patients with airway hyperreactivity are more sensitive. People living in urea–formaldehyde-insulated homes have experienced similar findings [8] and levels exceeding 1 ppm have been found many months or years after the original insulation, because the unstable resin releases its monomers. Liu et al. [9] found levels up to 0.46 ppm in mobile homes which have small volumes and extensive pressed-wood materials.

Formaldehyde is also a well-known sensitizer to the skin and/or the lung: contact dermatitis, and to a lesser extent, bronchial asthma have been reported in occupational and non-occupational settings [1–3]. However, sensitization appears to be rare even though formaldehyde is ubiquitous and skin contact unavoidable. In sensitized patients, anaphylactoid reactions can be induced by patch-testing with formaldehyde 1% in water [10]. Similarly, the use of dilute solution for the treatment of hepatic hydatid cysts has resulted in bronchospasm and shock with metabolic acidosis [11]. Formaldehyde may induce auto-immune reactions, including antinuclear autoantibody production [12] and membranous nephropathy with nephrotic syndrome [13].

The carcinogenicity of formaldehyde is still controversial, but more recent analyses seem to find an elevated lung cancer risk in exposed workers in industry [14]. Nasal cancer and malignant melanomas of the nasal cavity have also been reported [15]. The International Agency for Cancer Research (IARC) has classified formaldehyde as a probable human carcinogen (2A).

More recent findings about long-term toxicity include persistent neurobehavioral impairment in histology technicians [16] and people living in urea–formaldehyde-insulated homes [8]. Excessive fatigue, headache, memory loss, irritability, instability of mood, prolonged choice reaction time and altered cognitive functions were found in 4 patients exposed to 0.2–9 ppm [17].

Acetaldehyde and polymers

Acetaldehyde is a highly volatile colourless liquid used in the industrial production of acetic acid. Concentrated solutions cause chemical burns and

repeated contact can be followed by dermatitis without sensitization. Vapors above 50 ppm are irritating to the eyes and the respiratory tract. Systemic toxicity by ingestion includes narcotic action and sympathomimetic response with tachycardia, hypertension and hyperventilation [18]. Acetaldehyde is a metabolite of ethanol probably involved in several effects of both acute and chronic ethanol intake, namely facial flushing, liver injury, behavioural effects, fetal alcohol syndrome.

Paraldehyde is a liquid trimer used in the manufacture of dyestuff and as solvent for waxes, oils and resins. It is no longer available in Europe as an anti-epileptic drug but it is still in use as an hypnotic and in cough suppressants in the US. Therapeutic oral dosage is 5 to 10 ml (sedative) or 10 to 30 ml (hypnotic). Overdosage (more than 100 ml) produces mouth and abdominal pain, unconsciousness, coma, severe metabolic acidosis and collapse [19]. Toxic blood levels are in the range of 200–400 mg/l. Treatment is supportive. Paraldehyde addiction had also been reported during the treatment of alcoholism and withdrawal mimics alcohol withdrawal [19].

Metaldehyde is a solid cyclic tetramer actually used at low concentration, usually 5% or less as a molluscicide. Many cases of acute poisoning by ingestion of "meta-fuel" tablets have been reported, both in children and adults. Clinical features include nausea, vomiting, seizures and coma. Fever, renal tubular injury and liver necrosis have also been reported. In 1992, Moody and Inglis [20] described the suicidal ingestion of 35–50 ml of a 20% metaldehyde liquid molluscicide: serum levels remained elevated for 35 hours, with an apparent half-life of 27 hours, although it is generally held that depolymerisation to acetaldehyde is responsible for most of the toxic effects.

Glyoxal and glutaraldehyde

These two aliphatic dialdehydes are highly effective biocides widely used in the cold sterilization of medical, surgical and dental equipment. In France, they are often included together in commercial products [21]. Adverse effects occur mainly in hospital workers: headache, irritating symptoms of the eyes, skin and respiratory tract [22], even when ambient levels are below occupational limits (TLV = 0.2 ppm in most countries). Wiggins et al. [23] reported an unusual case of recurrent epistaxis associated with upper respiratory tract irritation and skin rash when handling a 50% glutaraldehyde solution. Inadequate rinsing of a Hoskin lens after soaking in 2% buffered glutaraldehyde resulted in keratopathy without long-term sequelae in a 88-year-old woman [24]. Glutaraldehyde and to a lesser extent glyoxal are also strong sensitizers: allergic contact dermatitis [25] and occupational asthma have been documented in health care workers [26] and radiographers [27]. Recently, systemic toxicity was suggested by 7 patients occupationally exposed to glutaraldehyde who experienced work-related tachycardia and palpitations; in 2 of them, ECG was obtained while they were symptomatic and showed supraventricular tachycardia [28].

Acrolein

Acrolein is a highly volatile yellow liquid, mostly used for the production of acrylic acid and acrylate esters. Non-occupational exposure occurs via cigarette smoking, house fires, car exhaust, heating of animal or vegetable oils, and treatment with cyclophosphamide. Acrolein is highly corrosive to the skin, the eyes and the respiratory tract, more so than formaldehyde. 1% solutions cause chemical burns. Ocular irritation starts from 0.15–0.25 ppm and one cannot withstand 1 ppm [29]. Inhalation results in ARDS with massive cellular desquamation of the bronchial lining and possibly death [30]. In 1993, Mahut et al. [31] reported one case of severe intoxication in a 27-month-old child after 1-hour inhalation of smoke from vegetable oil burning in his parents' kitchen. 18 months later, the boy experienced permanent productive cough, and CT scan showed emphysema, localized atelectasis and diffuse bronchiectasis.

No data on the long-term effects of acrolein in humans are available.

Furfural

Furfural (2-furaldehyde) is a oily liquid with an aromatic odour, used as a solvent and raw material in the manufacture of phenol–formaldehyde–furfural resins, and in foundries for the preparation of molds for metal castings. In humans, furfural is metabolized to furoic acid, a natural component of urine, with a high elimination rate in heavy drinkers of coffee. Like other aldehydes, furfural is irritant to the skin, eyes and respiratory tract. Seizures and cytolytic hepatitis have been described in early case reports. Sensitization (dermatitis, rhinitis, asthma) can also occur in occupational settings, for example in foundry workers [32].

ESTERS

Esters result from the condensation between carboxylic acids (R–COOH) and alcohols (R–OH) with water elimination. Most common are the esters from acetic, acrylic, methacrylic and phthalic acids.

Acetates

Methyl, ethyl, isopropyl, N-butyl, isobutyl, vinyl, etc. acetates are volatile liquids used as solvent. Published data on human acute poisoning or chronic exposure are scarce; toxicity is expected to be similar to petroleum hydrocarbons. Ethyl acetate is hydrolyzed in ethanol in animals and probably in humans.

Acrylates, methacrylates and cyanoacrylates

Acrylates, methacrylates and cyanoacrylates are unsaturated highly reactive monomers of polyacrylic resins used in paints and varnishes, sealants, adhesives and glues, textile fibers, plexiglas, photoprinting inks, and so on.

Medical uses include corneal lenses, dental prostheses and bone cement in orthopedics. Acrylate and methacrylate monomers are strong irritants for the skin, eyes and respiratory tract. They are now considered the fourth most common cause of contact (or airborne) sensitization due to resins in occupational settings [33]. In 1992, Kanerva et al. [34] reported an occupational pharyngitis in a female dentist handling acrylics: she had no skin symptoms but strong positive patch-test reactions to several acrylates. Skin sensitization with domestic exposures (nail varnish hardener, clothing) [35] and allergic contact stomatitis in denture wearers [36] can also occur. Occupational asthma is mainly caused by methacrylates, with several case reports in dental and orthopedic workers. Pneumoconiosis without fibrosis was described in 1989 in a 27-year-old dental student [37]: abundant acrylic material was found in the cytoplasm of macrophages; removal from exposure resulted in clinical improvement without sequelae. The neurobehavioural effects of methacrylates have been reported in dental technicians with evidence of systemic absorption [38].

Phthalates

Dimethyl, diethyl, dibutyl, diethylhexyl phthalates are oily liquids with low volatility used as plasticizers that soften resins without reacting chemically with them. Polyvinyl chloride products are mainly concerned. Published data on human acute and chronic toxicity are very few. They are moderate irritants for the skin, eyes and respiratory tract, but sensitization does not seem to occur. Symptoms and signs of polyneuropathy have been reported in phthalate production workers in 2 studies, without convincing evidence of a causal relationship [39]. Diethylhexyl phthalate (DEHP) has been involved in 3 cases of hepatitis in hemodialysis patients with terminal renal failure, due to migration of DEHP from blood PVC plastic bags [39].

KETONES

Ketones (R–CO–R′) are widely used organic solvents, either alone or most frequently in solvent mixtures. Exposure occurs mainly in occupational settings (manufacturing processes, degreasing operations, adhesive coating, painting, dry cleaning) but domestic poisonings are of concern with children drinking amounts of nail polish removers. Cyclohexanone is used predominantly for the synthesis of raw materials used in the production of Nylon. Acute toxicity is close to that of petroleum hydrocarbons, with pronounced narcotic effects. Accidental ingestion of 50–100 ml of methyl ethyl ketone peroxide, a polyester resin curing agent, resulted in corrosive burns, unconsciousness, severe metabolic acidosis, rhabdomyolysis, and fatal massive peripheral zonal hepatic necrosis [40]; the mixture also contained dimethylphthalate which could not be found by gas chromatographic examination of blood, urine and liver samples obtained 6 days post-mortem. In 1991, Welch et al. [41] reported an unusual case of dementia

and cerebellar ataxia following acute exposure to a solvent mixture of toluene and methyl ethyl ketone; two and a half years later, cognitive and behavioural changes were still present, without any alternative diagnosis.

Long-term effects include chronic neuropsychological and neurological impairment (psycho-organic syndrome) and polyneuropathy with methyl N-butyl ketone [42]. Many ketones (e.g. methyl ethyl ketone) increase microsomal cytochrome P-450 enzyme activities and potentiate toxicity of other solvents undergoing metabolic activation (e.g. carbon tetrachloride, trichloromethane, n-hexane and methyl N-butyl ketone).

ETHERS

Aliphatic ethers

Aliphatic ethers (R–O–R′) are highly flammable volatile solvents and chemical intermediates. Acute toxicity includes moderate irritation of the skin, eyes and respiratory tract, and marked CNS depression. Diethyl ether is still in use for degreasing the skin; divinyl ether has been used as an anesthesic agent, with adverse effects such as myocardial hyperexcitability and cytolytic hepatitis. Methyl-tert-butyl ether (MTBE) and ethyl-tert-butyl ether (ETBE) are used as octane boosters in lead-free gasoline with concentrations ranging from 5 to 10%. Since 1985, MTBE has also been used for dissolving cholesterol gallbladder stones. Efficacy and safety appeared to be good in a German clinical study involving 120 patients [43], but Ponchon et al. [44] reported one case of coma, hemolysis and acute renal failure 5 hours after instillation of 15 ml MTBE.

Bis-(chloromethyl)-ether (BCME) formation can occur when formaldehyde and chloride are released in the workplace atmosphere in various occupational settings (e.g. textile industry, photography, histology laboratories...). BCME has been recognized as a human carcinogen inducing small-cell carcinoma of the lung in exposed workers [45].

Tetrahydrofuran

Tetrahydrofuran (THF) is a cyclic ether which can dissolve many types of plastic materials; its applications grow steadily. On contact with air, THF may form peroxides which increases its irritating effects. Garnier et al. [46] described 2 cases of poisoning with headache, nausea, chest pain, cough and cytolytic hepatitis after occupational exposure in confined spaces. Seizures, possibly related to metabolic transformation in γ-butyrolactone, have been reported. Long-term effects in humans are unknown.

Glycol ethers

Glycol ethers are a family of organic solvents widely used in both industrial products (e.g. paints, resins, lacquers, inks, paint and varnish removers, pesti-

cide formulations) and household products (e.g. detergents, window cleaning solutions). Miscibility in both water and organic solvents and low volatility are their basic properties. Monoalkyl ethers of ethylene glycol are metabolized via alcohol- and aldehyde–dehydrogenases to their respective alkoxyacetic acids, which are the primary toxic agents [47].

Gijsenbergh et al. [48] described the suicidal ingestion of about 500 ml of a window cleaning agent containing 12.7% butylglycol and 3.2% ethanol resulting in coma, hypotension, severe metabolic acidosis, and slight hemolysis with hematuria. Renal function was never impaired and urinary oxalate excretion remained normal, although an accessory pathway to ethylene glycol has been suggested [49]. Butylglycol half-life was 210 mn. One additional case was reported by Bauer et al. [50] in a chronic alcohol abuser who experienced ARDS from an unknown mechanism after massive ingestion. Conventional management includes gastric aspiration, hemodialysis and supportive care. In 24 pediatric cases of glass cleaner ingestions (containing 0.5 to 9.9% butylglycol) reported to the Pittsburgh Poison Center during 5 months in 1991 [51], all children remained asymptomatic, including 2 who ingested more than 15 ml and were treated by gastric emptying.

Chronic toxicity occurs in the workplace and may include CNS effects, bone marrow suppression, oligospermia and possible reproductive adverse effects [47]. Reversible macrocytosis and lymphocytosis were found in 3 young women in a glass frame factory [52]. Teratogenicity and fetotoxicity noted in animals have not been clearly demonstrated in humans. In occupational settings, biomonitoring is a better way to assess exposure than atmospheric sampling because dermal absorption is the main route of intake and the efficacy of protective gloves is often inadequate.

AMINES

Aliphatic amines

Aliphatic amines are volatile liquids with an ammoniacal odour. Aqueous solutions are strongly alkaline. They are very common in the chemical and pharmaceutical industry, and in many occupational settings (e.g. catalysts in polymer production, coremaking process in foundries, cutting oils in metallurgy). Irritant, or corrosive, properties of most aliphatic amines are well-known, resulting in chemical burns. Transient visual disturbances such as haze due to corneal oedema and mydriasis or cycloplegia have been reported in workers exposed to low or moderate tertiary aliphatic amines levels, as well as experimental exposure in volunteers [53]. High rates of skin and respiratory sensitization were found in employees exposed to ethylene amines in a chemical plant [54]. Occupational contact dermatitis can also occur in heath care workers [55] and patients, as ethylenediamine (EDA) is present in aminophylline and some topical drugs. In 1973, Niveau [56] reported the case of a

36-year-old worker splashed with large high-pressure amounts of EDA. Red-brown generalized erythema and anuria appeared 4 hours later, and he died 55 hours after the accident. Pathogenesis remained unclear, probably massive hyperkalemia induced by hemolysis.

Aromatic amines

Aromatic amines are oily liquids or solids with rather low volatility. Industrial uses include the manufacture of dyes and drugs, curing of epoxy and polyurethane resins, rubber vulcanizing, developers in photography, etc. Aniline and O-toluidine are found in cigarette smoke.

Aniline and related compounds are potent methemoglobin-forming agents, by oxidizing iron to the ferric state. Acute exposure results in methemoglobinemia with headache, weakness, cyanosis and coma. Despite protective measures, acute poisonings are still reported in the occupational setting [57], most often via the cutaneous route. Domestic poisonings have become anecdotal since aromatic amines have been banned from household products, but sometimes the chemical is taken home by workers and accidentally ingested by a child, as in Mier's report [58]. Van der Vorst [59] described 3 cases of methemoglobinaemia (14.5 to 43.5%) in premature neonates nursed in the same type of incubator: they inhaled p-chloroaniline produced by the decomposition of chlorhexidine gluconate inadvertently used as a humidifying fluid. The management of acute poisoning includes methylene blue infusion when methemoglobinemia is above 30%. Response to repeated methylene blue administration may be insufficient if the dose is high and/or if G_6PD-deficiency is present, and exchange transfusion has then proved successful [58].

Carcinogenicity is the striking risk of chronic exposure to aromatic amines in the workplace and indeed some (e.g. 4-aminodiphenyl, auramine, benzidine, β-naphthylamine, O-dianisidine, methylene bis O-chloroaniline) are potent bladder carcinogens. Tumor induction is clearly related to the duration of exposure with a 30-fold increased risk of dying from bladder cancer after 6 months or more of exposure in dye factories [60]. Despite restrictions of use, bladder cancers are still being reported: between 1982 and 1990, Popp et al. [61] detected 7 cases of bladder cancer in a group of 49 workers exposed from 1965 to 1976 to 4-chloro-O-toluidine while synthetizing the insecticide chlordimeform. N-acetylation is a detoxification process, and 5 of these 7 patients were found to be slow acetylators.

Hepatotoxicity have been demonstrated with 4,4'-methylenedianiline (MDA) in both non-occupational ("Epping Jaundice" in 1965 in the UK) and occupational settings, for example the. production of isocyanates and curing of epoxy resins. Clinical and biochemical findings included jaundice, dark urine, fever, elevated serum bilirubin, alkaline phosphatase, transaminases and eosinophil count, and cholestasis shown by percutaneous liver biopsy. Long-term follow-up of 10 intoxicated workers resulted in one case of bladder cancer versus 0.05 expected case [62], but the smoking status was not known. As MDA

is closely related in structure to benzidine, this finding could indicate that MDA is also a human carcinogen.

Other effects of aromatic amines in exposed workers include allergic contact (or airborne) dermatitis, and to a lesser extent, occupational asthma. Yellow staining reactions of the skin, nails and hair have been described among workers engaged in molded plastic operations involving MDA [63].

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Human Toxicology, J. Descotes (Ed.)

Ph. Hantson, F.J. Baud and R. Garnier

26. Toxic gases

Acute exposure to toxic inhalants under occupational or accidental circumstances may lead to a large variety of clinical manifestations, some of them being particularly life-threatening. The chronic effects of acute exposure have not been fully characterized. In this review, toxic gases will be classified according to the mechanism of injury, either as irritant or as asphyxiant. The clinical manifestations following fume or smoke exposure will be presented briefly.

IRRITANT GASES

Ammonia

Ammonia is widely used in the industry and as a household cleaner. Mixing ammonia with hypochlorite bleaches results in the formation of chloramine causing partially reversible pneumonitis.

The inhalation of ammonia vapors causes irritation of the eyes and respiratory tract. Dyspnea with bronchospasm, cough, hemoptysis, chest pain are the main clinical features. Mucosal burns develop along the tracheobronchial tree [1]. Hypoxemia with pulmonary edema and altered mental status often complicates exposure to concentrated ammonia vapors. Persistent pulmonary damage may follow an apparent clinical improvement [2]. Other symptoms include irritant effects with nausea, vomiting, burning sensation, swelling of the lips, mouth and larynx.

No reliable data exist regarding the effects of prolonged exposure to ammonia gas [3]. According to available data, ammonia seems not to be carcinogenic.

Bromine

Bromine gas is very corrosive to the eyes, skin and respiratory tract. Pulmonary toxicity seems to be even more severe than that of chlorine gas and may also evolve to chemical pneumonitis and ARDS [4]. Neurologic and gastrointestinal manifestations can also be encountered. Dermatitis and burns may result from inhalation exposure.

Toxicity following chronic exposure may be similar to that observed after ingestion of excessive amounts of bromides. A mild degree of spermatogenesis suppression and impaired reproductive performance were observed in a recent series of eight patients following accidental exposure to bromine vapor [5].

Chlorine and hydrogen chloride

Acute chlorine gas exposure is commonly due to the manipulation of household cleaning agents. Chlorine gas is converted to hydrochloric acid and active oxygen. Chlorine gas is corrosive to mucous membranes. Nose, throat and eye irritation is frequent. Burning, chest pain, suffocation, coughing are typical findings following mild to moderate exposure. Severe pulmonary edema is usually seen 12–24 hours after massive exposure and respiratory arrest is possible [6]. Delayed airway hyperresponsiveness has been noted after acute exposure [7]. This pattern was mainly identified among nonsmoking subjects in a recent study [8].

Hydrogen chloride shares the same corrosive properties as chlorine. Respiratory effects may range from irritation or even ulceration of the upper airways to reversible respiratory obstruction; laryngospasm, non-cardiogenic pulmonary edema and hemorrhage were infrequently observed. Inconsistent alterations of pulmonary function were reported following chronic or prolonged exposure. Long-term sequelae of acute exposure are less documented.

Fluorine

Fluorine is also considered as an irritant and may cause major cutaneous burns. Eye, nose and respiratory tract irritation is frequent. Pulmonary complications are usually severe with bronchospasm and pulmonary edema [9].

Osteosclerosis has been reported following very long occupational or environmental exposure [10]. No teratogenic effects have been observed in mice.

Iodine

Iodine is available in solid forms or in vapors. Liquid formulations of iodine are still widely used as antiseptic preparations. Iodine is metabolized to iodide which can be stored as thyroglobulin in the thyroid gland [11]. Iodine is toxic by ingestion or inhalation. Corrosive properties directly result in severe gastroenteritis with cardio-circulatory collapse, CNS manifestations or renal failure. Inhalation of iodine vapors may lead to irritation of the respiratory tract. Hypo- or hyperthyroidism may develop following long-term iodine exposure (topical applications of povidone iodine). There is also evidence that iodides diffuse across the placenta and into the breast milk.

Nitrogen derivatives

Nitrous oxide (N_2O) is an inorganic gas widely used for clinical anesthesia and as propellant in the industry. Acute toxicity following N_2O inhalation is

due to asphyxia, with fatalities reported among sniffing abusers [12]. Recent reports showed that prolonged anesthesia with N_2O in normal patients is devoid of clinical side effects [13].

Conflicting data exist concerning teratogenicity in humans. A greater incidence of spontaneous abortion in exposed dental assistants has been reported. Occupational exposure to high levels of nitrous oxide may adversely affect women's fertility [14].

Animal studies suggest that N_2O is a potential carcinogen.

Nitrogen oxides. Nitrous oxide fumes are mixtures of varying proportions of five oxides: nitric oxide (NO), nitrogen trioxide (N_2O_3), nitrogen dioxide (NO_2), nitrogen tetroxide (N_2O_4) and nitrogen pentoxide (N_2O_5). Silo-filler's disease results also from the decomposition following fermentation of nitrous acid into a mixture of nitrogen oxides.

Pulmonary damages are mainly observed following acute or chronic exposure to nitrogen oxides. Coughing, shortness of breath on exertion or at rest, chest pain and hemoptysis were present in an outbreak of NO_2-induced respiratory illness among ice hockey players [15]. Delayed pulmonary edema (4 to 24 hours) is commonly encountered [16]. Respiratory manifestations include bronchospasm and bronchiolitis obliterans, the late-onset form of which is more severe and hardly reversible [17]. Emphysema may occur after low and chronic exposure. Increased airway responsiveness to low levels of NO_2 in asthmatic subjects is controversial [18]. Other symptoms include fatigue, headache and nausea. Methemoglobinemia may occur in the presence of NO or higher oxides of nitrogen.

The teratogenic, genotoxic and carcinogenic effects of NO or NO_2 have only been recently reported in animals.

Ozone

Ozone can be produced either by ultraviolet light action on oxygen, by photochemical reactions or in the industry. Ozone has a high oxidative capacity affecting cell membranes. Its toxic effects may result from the formation of peroxides and free radicals. Ozone acts primarily as an irritant for the eyes, throat and respiratory tract. Respiratory manifestations include dyspnea, edema, bronchitis, bronchiolitis and alterations of pulmonary function tests with increased pulmonary resistances [19]. The effects of ozone on airway resistance when combined with other air pollutants is still a matter of debate.

Long-term effects have not yet been fully explored but epidemiological studies have provided evidence that chronic exposure to photochemical oxidants may deteriorate lung function [20]. Bronchiolitis and bronchitis have been reported in animals following chronic exposure.

Ozone could be genotoxic due to its radiomimetic properties. Teratogenicity has been observed in animal models following exposure to high concentrations. However, cytogenetic effects on human lymphocytes could not be demonstrated [21].

Phosgene

Phosgene is a highly toxic gas produced by the burning of chlorinated hydrocarbons or the action of ultraviolet radiation on such compounds. Phosgene reacts with water to form hydrochloric acid and carbon dioxide. It is considered as an irritant to the skin, eyes and respiratory tract. Following exposure to high concentrations, severe pulmonary complications may develop including pulmonary edema and bronchoconstriction. Delayed onset pulmonary edema with fatal respiratory failure has been reported [22]. Non-cardiogenic pulmonary edema may also be related to an increased pulmonary vascular permeability [23].

Phosgene can also impair renal and hepatic function by depleting glutathione stores [24]. Chronic exposure may lead to pulmonary fibrosis and emphysema [25].

Sulfur derivatives

Sulfur dioxide (SO_2) is formed by the combustion of sulfur-containing materials and is considered as an important air pollutant (acid rain).

SO_2 is irritating to the mucosa of the nasopharynx and respiratory tract. Respiratory symptoms are prominent with pulmonary edema and bronchoconstriction. Asthmatic patients are more susceptible and bronchial hyperactivity may persist for several years [26]. Obstructive and restrictive lung disease, chronic bronchitis may also develop after an acute exposure. Other symptoms include conjunctival irritation and dermal frostbite.

There is no evidence of teratogenic or direct carcinogenic effects due to SO_2 which could be a promoter in combination with benzo(a)pyrene or arsenic.

Sulfuric acid. Fuming sulfuric acid is a solution of sulfur trioxide in sulfuric acid. It is also present in mist and acid rain. Sulfuric acid is corrosive to the mucous membranes and respiratory tract. Inhalation of sulfuric acid mist causes a reflex increase in respiratory rate and bronchoconstriction. Overacute exposure produces severe bronchospasm and non-cardiogenic pulmonary edema [27].

ASPHYXIANT GASES

Carbon monoxide

Carbon monoxide (CO) is produced by the incomplete combustion of carbon-containing materials in poorly ventilated rooms. Inhalation and even ingestion of methylene chloride can also produce delayed CO poisoning.

CO intoxication should be determined from the patient's mental and cardiovascular status rather than carboxyhemoglobin level. In severe poisoning, arterial pH, bicarbonate levels, serum CPK activity and chest X-ray should be monitored.

Acute and chronic effects of CO poisoning are due to tissue hypoxia. The most sensitive organs to oxygen deprivation are the central nervous system (CNS) and the myocardium. Infants, pregnant women, elderly people or patients with a previous history of myocardial insufficiency or chronic obstructive pulmonary disease are particularly at risk. CNS depression may evolve to irreversible coma. Residual and delayed neurologic effects may occur after acute CO poisoning. Alteration of cognitive functions is the main feature. The incidence of delayed neurological sequelae is correlated to the initial level of consciousness and duration of coma. Myocardial insufficiency may be aggravated or precipitated by CO [28]. Pulmonary edema and adult respiratory distress syndrome have been observed. Other symptoms include psychiatric, gastrointestinal and metabolic disorders. The value of hyperbaric oxygen was assessed in a recent prospective study. Pregnant women were excluded from this study. In patients without initial impairment of consciousness, the value of hyperbaric oxygen was not greater than normobaric oxygen. In patients with initial impairment of consciousness, two sessions of hyperbaric oxygen were not more efficient than one session in the prevention of late neurological sequelae [29].

Potential effects of long-term exposure to low concentrations remain controversial. CO is teratogenic and embryotoxic at high maternal carboxyhemoglobin concentrations [30]. An increase in fetal death has been reported in a recent survey [31].

Carbon dioxide

Hypoxia from reduced oxygen concentration in inspired air is the consequence of acute exposure to simple asphyxiant gases. Symptoms appear usually when oxygen concentration is less than 15%.

In 1985, the Lake Nyos disaster was responsible for numerous deaths. It was due to a massive liberation of CO_2 as a suffocating aerosol leading to immediate asphyxia. Survivors had lost consciousness for several hours; some complained of cough, headache and weakness [32,33].

Exposure to lower concentrations results in hyperventilation and headache due to cerebral vasodilatation.

Cyanide derivatives

There are various sources of cyanide formation. The most toxic forms by inhalation are hydrogen cyanide (HCN), cyanogen [$(CN)_2$], and its halides, and cyanide salts. Cyanide can also be released by hepatic metabolism from various nitrile compounds resulting in delayed cyanide poisoning. Calcium cyanide, isocyanates and metal cyanides do not share the same toxic properties and act mainly as irritants.

Symptoms following acute poisoning depend upon the extent of and time since exposure. Cyanide exposure may produce death within minutes. Hyperpnea, tachycardia, hypertension and central nervous system (CNS) stimu-

lation may be seen in the early phase of cyanide poisoning before the stage of global depression. Cyanosis is only a late finding. Metabolic acidosis and elevated serum lactate levels are commonly noted. Victims of cyanide poisoning either die acutely or recover fully. Parkinsonian symptoms and dystonia have been reported after ingestion of cyanide salts [34]. Methyl isocyanate acts mainly as an irritant gas, and the fatalities in the Bhopal disaster were due to acute respiratory distress occurring in the area close to the factory.

Chronic cyanide exposure may produce various neurological disorders (headache, optic neuropathy, myelopathy). Effects on the thyroid gland (decreased iodine uptake) and on vitamin B_{12}/folate metabolism have also been suspected. Dermatitis and respiratory tract irritation are also possible.

Potassium cyanide has been associated with teratogenic and genotoxic effects in animals. Chromosomal abnormalities, spontaneous abortions and malformative syndromes have been demonstrated following the Bhopal tragedy [35].

Hydrogen sulfide

Hydrogen sulfide is a highly toxic gas which is produced by decomposition of sulfur compounds. It can be encountered in a large variety of industrial processes. At low vapor concentrations, hydrogen sulfide is irritant for the eyes, nose, respiratory and gastrointestinal tract. At higher concentrations, it produces neurological impairment with dizziness, headache and loss of consciousness [36]. Mortality following exposure to very high concentrations has been reported to reach 6% [37]. Respiratory paralysis, tachycardia with ECO ischemic changes, hypotension, cyanosis, asphyxial convulsions occur in fatal cases. Anoxic effects would be related to the inhibition of cytochrome oxidase enzymes. Lactic acidosis is a common observation following hydrogen sulfide poisoning. Delayed neuropsychiatric sequelae have been also reported after acute hydrogen sulfide poisoning [38].

Phosphine

Phosphine is a highly toxic gas produced by different phosphide salts (aluminium, calcium, zinc) following exposure to moisture. Phosphine is mainly used as fumigant or rodenticide. Toxicity occurs either following ingestion or inhalation. Organs with high oxygen requirements are especially sensitive, including the brain, kidneys, heart and liver. Mortality following aluminium phosphide poisoning remains particularly high [39]. The cardiovascular and respiratory complications are often life-threatening and include cardiac arrhythmias, shock and also delayed pulmonary edema.

Symptoms of chronic poisoning include anemia, bronchitis, gastro-intestinal and neurosensorial disturbances [40].

OTHER TOXIC GASES

Metal fume fever

Metal fume fever is produced by inhaling metal oxides produced by heating various metals, the most common being zinc and copper. Non-specific symptoms including fever, dry throat, pyrexia, myalgias, weakness or dyspnea are commonly reported; a metallic taste is inconstant. Recovery is usually complete within 24 to 48 hours with no chronic impairment [41].

Polymer fume fever

When polytetrafluoroethylene (Teflon®) is heated up to 315–375°C under conditions of insufficient ventilation, an influenza-like syndrome called polymer fume fever can develop. Polymer fume fever is usually self-limiting with a complete resolution within 48 hours. Symptoms may start up to 12 hours following exposure and are usually less severe than in metal fume fever. They include hyperpyrexia, mild tachycardia and hypertension, chest discomfort with respiratory tract irritation and weakness. Interestingly, no fatalities have been reported and there is no evidence of long-term effects [42].

Products of combustion

Symptoms following fire hazards often combine effects of irritants (acrolein, ammonia, chlorine, hydrogen chloride, nitrogen dioxide, phosgene, sulfur dioxide) and asphyxiants (carbon monoxide and cyanide). Smoke, heat and flame may all play a deleterious role. Thermal injury mainly affects the upper airways and can be used as a marker for significant smoke exposure. Smoke is composed of a particulate fraction and gases. Toxic gas production depends on oxygen supply, temperature, rate of heating and material. Cardiovascular, respiratory and central nervous systems may be variably affected.

Early recognition of signs of severe exposure to CO and CN is of primary importance, since specific therapy can be added to the general supportive measures, even at the scene of fire [43,44].

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27. Corrosives

INTRODUCTION

Corrosives (or caustics) are strong alkalis and/or acids which cause tissue destruction. Acids produce a coagulation necrosis that tends to cause a superficial type of damage rather than a deep, penetrating type of burn. Alkalis tend to cause a deep and penetrating necrosis which often results in severe effects such as oesophageal perforation. These deeper burns are associated with much severe scarring and stricture formation.

Corrosives are used for household, industrial and commercial purposes. Those used for household purposes include toilet and drain cleaners which contain 80–90% sulphuric acid or 96–100% sodium or potassium hydroxide, 10–25% hydrochloric acid, 2% oxalic acid and 0–100% sodium bisulphate; metal cleaners and antirust compounds contain mainly phosphoric acid (5–80%), hydrochloric acid (5–25%), sulphuric acid (10–20%) and chromic acid (5–20%); automobile battery acids contain sulphuric acid (25–30%), swimming pool sanitizers contain calcium or sodium hypochlorite (70%) and household bleaches 3–6% sodium hypochlorite, which seldom causes more than minor mucosal erosion in contrast to the highly concentrated swimming pool sanitizers.

Ammonium hydroxide concentrations range from 3% (weaker solutions) to 10% (potentially corrosive). Automatic dishwashing detergents contain products such as sodium tripolyphosphate, sodium metasilicate, sodium silicate, and sodium carbonate, which produce corrosive lesions. Clinitest tablets contain mainly citric acid, sodium hydroxide, and sodium carbonate. Injury occurs by both direct corrosive action and an exothermic heat reaction. Commonly damaged sites include the proximal oesophageal mucosa and, occasionally the gastric and duodenal mucosae. Oven cleaners products contain sodium hydroxide.

Some bleaches contain 15–17% silicate and 60% sodium carbonate, and have a pH around 10.5. Granular commercial bleaches may contain higher concentrations of hypochlorite or carbonate leading to greater tissue destruction.

Industrial uses of corrosives include plating, chemical and dyestuff and cement manufacturing, leather tanning, and photography with chromic acid. Solutions weaker than 10% hydrochloric acid are used as a bleaching agent whereas concentrated solutions (36%) are involved in dye and chemical synthesis,

metal refining and the plumbing industry. Commercial uses of nitric acid include engraving (63%), metal refiners and fertilizer manufacturing whereas phosphoric acid solutions (85–90%) are used in metal cleaning, and rust proofing. Concentrated solutions of hydrofluoric acid (90%) are used in petroleum refining, antimony fluoride extraction, synthesis of pharmaceuticals and germicides, removal of metal casing and as an anhydrous catalyst for high-octane gasoline.

Most toxic-related emergencies due to corrosives result from accidental exposure to household products such as toilet bowl cleansers and metal cleaners. Although acid ingestions are less common than alkali ingestions, morbidity and mortality (18%) are worse for acid ingestions. This more severe toxicity probably reflects the more intentional nature of acid ingestions in adults since severe pain often limits casual childhood exposures. However, accidental caustic ingestion is frequent in children and can result in severe sequellae [1,2]. Hydrochloric acid and sulphuric acid are the most common agents ingested, with gastric sequelae more common with hydrochloric acid because of the lower survival rate for sulphuric acid-induced perforation.

The ingestion of corrosive substances in adults compared with the ingestion in children, tends to be more severe, because the intent is often suicidal rather than accidental [3,4]. The severity and extent of damage produced to the gastrointestinal tract depends on the morphological form of the caustic agent. In the acute stage, perforation and necrosis may occur. Long-term complications include oesophageal stricture, antral stenosis, and the development of oesophageal carcinoma which occurs up to 40 years after the time of injury [3]. X-rays of the abdomen and chest should be done initially to detect any evidence of perforation. Endoscopy should be performed as soon as possible to evaluate the extent and severity of damage, unless there is evidence of perforation. A complete examination is feasible in most cases. Stricture formation is more common in patients with second and third degree burns [3]. Adults may commonly have oesophageal injury, but injury in children may be economically devastating [5].

Exposure to corrosives may result in severe burns depending on the determinants of toxicity, i.e. the type of substance ingested, pH, volume ingested, concentration, contact time, volume of liquid material in stomach, toxicity for the pyloric sphincter and exothermic reactions (alkali). Crystals or solid granules produce burns in the oropharynx and 10–30% are associated with oesophageal lesions. Liquids are rapidly swallowed and injure more mucosal surface resulting in greater liquefaction, and oesophageal burns may occur in up to 100% of cases. Concentration is more critical than volume. Concentrations of 30% and more are associated with higher morbidity and mortality.

TOXICOLOGICAL MECHANISMS AND STAGES OF INJURY

Alkali corrosives damage the gastrointestinal tract by liquefaction necrosis, whereby the saponification of fats and solubilisation of proteins allow deep penetration into tissues. In contrast, acids cause a coagulation necrosis with

the formation of protective eschars, whereas alkalis cause continuing damage after exposure because of their ability to penetrate tissue and produce continuing vascular thrombosis and necrosis. It has been recently postulated that, in addition to its corrosive action, monochloroacetic acid probably blocks the tricarboxylic acid cycle (Kreb's Cycle) and may also react with sulfhydryl groups in enzymes, causing severe tissue damage in energy-rich organs [6].

Concentrated solutions of caustic material can produce transmural necrosis with exposures as short as one second. Burns of the oesophagus classically follow three pathophysiological phases which characterise both acid and alkali ingestions as indicated below:

– **Acute inflammatory phase** (3–7 days): this is characterised by oedema, erythema, vascular congestion. Thrombosis and necrosis occur and the peak is reached within the first 48 hours. In case of burns due to acids, the necrotic mucosa sloughs by the 3rd or 4th day and an ulcer forms.

– **Latent granulation phase** (up to 14 days): fibroblast granulation tissue fills after mucosal sloughing, and collagen deposition follows. Oesophagoscopy is contraindicated as the oesophagus is especially vulnerable to perforation.

– **Chronic cicatrisation phase** (several weeks to years): scar tissue replaces the defect, which can lead to symptomatic oesophageal obstruction. Severity of the lesion and outcome are related to the type of the corrosive, its concentration and amount and to the duration of exposure.

Clinical features

A 38-year-old man was splashed with a 80% monochloroacetic acid solution on 25–30% of his body surface. In addition to epidermal and superficial dermal burns, features of systemic poisoning occurred within a few hours including disorientation, agitation, cardiac failure and coma. He later developed severe metabolic acidosis, rhabdomyolysis, renal failure and cerebral oedema, and died due to uncal herniation on the 8th day. The 4-hour post-exposure plasma monochloroacetic acid concentration was 33 mg/l, confirming skin absorption [6].

Oesophageal intramural pseudo-diverticulosis (OIP) was observed in 14 patients (23.7%) in a radiological study involving 5 patients with sequelae of corrosive acid injury of the upper gastrointestinal tract evaluated over a 5-year period [7]. OIP is a rare condition characterised by multiple, small flask-shaped diverticula in the oesophageal wall, and best demonstrated on single-contrast barium examination. Oesophageal stricture was a constant association, and the diverticula tended to involve either the entire length of the stricture or its upper part. There was however no correlation between the length of the stricture and number of diverticula ($p > 0.05$). Endoscopic dilatation resulted in relief of dysphagia, and the diverticula regressed in number. These observations suggest that OPI is a common sequellae of oesophageal acid injuries and diverticula tend to form at the site of initial contact between acid and susceptible oesophageal mucosa [7].

A unique type of burn injury has been reported by Winemaker et al. [8] in three patients who sustained it while working in the pulp and paper industry in Canada. These patients suffered combined chemical (pH 11–13) and thermal (85–95°C) injuries when exposed to "black liquor", a solution which is used in this industry to convert wood chips to pulp. Black liquor can rapidly cause devastating thermal-corrosive burns to the skin, eyes, lungs, and upper gastrointestinal tract. The first patient sustained a relatively minor full skin thickness 3% body surface area (BSA) injury to both feet and lower legs. The second patient who was sprayed with heated black liquor solution, sustained a full skin thickness injury to 40% BSA and also suffered virtual loss of vision in one eye. The third patient who was sprayed with the solution, sustained a 98% full skin thickness burn and severe inhalation injury, and died during day one postburn.

The respiratory effects of industrial exposure to sodium hydroxide have been recently observed in a 63-year-old man [9] who was working daily for 20 years cleaning large industrial jam containers by boiling lye solution without using respiratory protective equipment. Physical examination, chest X-ray film, pulmonary function tests, and arterial blood gases were all compatible with severe obstructive airway diseases with significant air trapping. It is probable that this massive and prolonged occupational exposure to the corrosive effect of NaOH mists induced irritation and burns to the respiratory system, eventually leading to severe obstructive airway disease [9]. Likewise, corrosive lung injuries caused by exposure to sodium hydroxide have been described in a formerly healthy 25-year-old man who developed irreversible obstructive lung injury after working for one day with a caustic soda treatment of wood in a poorly ventilated room [10]. A rare case of chemical burn of the tracheobronchial tree with powdered sodium hydroxide in a child has been recently reported [11]. In the course of the child's condition there were several periods of acute respiratory failure, requiring respiratory resuscitation with intubation, mechanical ventilation, aspiration and kinesitherapy. The chemical burn was followed by several hours of imaginary well-being, but subsequently pulmonary oedema developed. On the 5th day obstruction of the air passages by secretions and mucosal hyperemia led again to acute respiratory failure. On the 15th day bleeding from the mucosa of the respiratory and gastrointestinal tracts developed. Knowledge of these periods in the pathophysiological process leading to acute respiratory failure and adequate respiratory resuscitation are a prerequisite for a favourable outcome of the morbid process [11].

A case of fatal poisoning in a one-year-old girl after ingestion of a household cleaner containing 4.5% sodium hypochlorite (klorin) in an alkaline solution (pH = 12) has been recently reported [12]. The forensic medical and toxicological investigations were supplemented by animal studies. These studies indicate that 5, 10 and 15 ml klorin/kg given to rats are highly toxic, and that local tissue damage and secondary systemic involvement develop with a severity corresponding to the amount administered. All rats died and showed various degrees of degeneration and necrosis of the oesophagus, changes analogous to those found at the autopsy of the child [12].

Inhalation

Inhalation of chlorine gas with toxicity to at least 14 persons occurred at two state hospitals in California [13]. These episodes involved the mixture of bleach (sodium hypochlorite) and a phosphoric acid cleaner, which released chlorine gas and other chemical by products.

A housewife cleaned toilet porcelain connected directly to a sewage storage tank with a mixture of cleaning agents: sodium hypochlorite and hydrochloric acid solutions. She complained of insomnia on the night after cleaning and suffered from severe metabolic acidosis [14]. She received carbonate transfusion, plasmapheresis and plasma exchange. Permanent blindness ensued, however, from the third day after the event suggesting that other chemicals might have been the causative factor.

Dental interventions

The inadvertent injection of sodium hypochlorite into the cheek of a patient during irrigation of the right maxillary central incisor root resulted in pain, oedema, and necrosis of the subcutaneous tissues and mucosae [15]. Surgery was necessary to contain the destructive process which extended from the upper lip to the right eye. The histopathological examination demonstrated the high cytotoxicity of sodium hypochlorite on vital tissues.

In endodontic treatment, solutions of sodium hypochlorite are widely used as an irrigating agent. It is an effective solvent of both necrotic and vital tissues, but too toxic to the surrounding tissues. The acute symptoms caused by the toxic reaction of sodium hypochlorite have been reported in three patients [16]. Similarly, a midroot perforation was created and sodium hypochlorite was extruded through the opening into the supporting tissues.

Zargar et al. [17] reported that clinical signs do not give a reliable forecast of the extent and severity of injury, in a prospective study of 31 patients who ingested strong alkalis, i.e. sodium hydroxide and potassium hydroxide. The oesophagus was injured in all patients, the stomach in 93.5% and the duodenum in 29.6%. Acute complications occurred in 32.3% and death in 12.9%, all but one of such patients had grade 3 burns. The corrosive burns were classified as grade 2a in six patients, grade 2b in eight and grade 3 in 12. All patients with 2a injury recovered without sequelae. Four of the eight patients with grade 2b injury and all survivors of grade 3 injury developed oesophageal or gastric cicatrisation, or both, which required endoscopic or surgical treatment. Endoscopy was found to be not only a safe and reliable tool for diagnosis in such patients but also of importance for treatment and prognosis. Therefore the ingestion of strong alkali is a very severe condition that inflicts severe contiguous injury to the oesophagus and stomach, and results in high morbidity and mortality.

Corrosive agents and commonly prescribed medications have been recently reported to be the probable cause of ulcerative oesophagitis [18] in five adoles-

cents after ingestion of tetracycline preparations with minimal water immediately before going to bed.

The severity and extent of damage to the gastro-intestinal tract produced by corrosive substances depend on the morphological form of the caustic agent. In the acute stage, perforation and necrosis may occur. Long-term complications include oesophageal stricture, antral stenosis, and the development of oesophageal carcinoma [3].

Forty-five cases of which 13 had a fatal outcome, of acute accidental poisoning with a disinfectant, which contains a mixture of quaternary ammonium compounds, have been reported to the Paris Poisons Centre [19]. All the victims were mentally disturbed patients two of whom were young adults hospitalised in psychiatric units and the other 43 were old people hospitalised for senile dementia. All patients ingested the solid preparation which was left in their room by hospital workers who did not realise it was dangerous. Corrosive burns of the mouth, pharynx, oesophagus and sometimes of the respiratory tract were produced in most patients. Thirteen of them died, all of whom were old patients. Ten of the patients had inhalation pneumonitis and died of acute respiratory distress one hour to 12 days after taking the powder. Progressive deterioration was responsible for the death of the other three between the 19th and 40th days. These severe accidental poisonings could be easily prevented by a better information of hospital workers, and by storing the disinfectant and preparing the solution beyond the reach of patients.

MANAGEMENT

Lesions caused by ingestion of corrosive substances have so far been treated at the time of sequelae. The first step of the treatment is fasting, fluid replacement, and analgesics if required. A full examination must be performed, especially in the throat, even though there is no strong correlation between early clinical signs and the severity of the lesions. Blood samples must be obtained to look for metabolic acidosis, hyperleukocytosis, hemolysis and consumption coagulopathy, which could be better indications of the severity. Fiber optic endoscopy of the upper digestive tract should be performed as soon as the physical and psychological condition of the patient is stable; if possible before the 12th hour and no later than the 24th hour [20].

Corrosive strictures of the oesophagus are common, and being long and dense they frequently require surgical replacement of the oesophagus [21]. A method of mid-colon segment, from the mid-ascending to the mid descending segment, was performed in 33 patients. The conduit was placed retrosternally in 27 patients and subcutaneously in the rest. There was no mortality and there was no instance of colonic necrosis. The procedure restored an ability to eat normal food in 93.9% of patients compared to only 39.2% of patients with bullgienage [21].

Oesophageal replacement with an interposed graft of the large intestine on a vascular pedicle between the cervical oesophagus and oesophageal stump

over the diaphragm was performed in four children for Vogt's classification Type I and II oesophageal atresia [22]. A tracheo-oesophageal fistula was closed in three, and gastrostomy was established in four neonates to provide nutrition. Oesophageal replacement was performed in patients aged 2 years and 5 months, to 5 years and 4 months. One girl died following oesophageal replacement from bilateral pneumonia. A non-functional oesophagus was extirpated for corrosive oesophageal stricture with simultaneous replacement by means of colonoplasty in two boys aged 3.25 years and 3.5 years. The patients were followed for 3 to 12 years after oesophageal replacement; their ability to swallow, psychomotic development and surgical criteria were used to evaluate the outcome as excellent in four, and good in one of the children [22].

The most common cause of oesophageal stricture in children is the accidental ingestion of strong corrosive agents. Two hundred and two children of whom 145 were male (71.7%) and 57 female (28.3%) with 168 (83.2%) younger than 6 years of age, were evaluated retrospectively between 1976 and 1989 at the Ankara's Hacettepe University Children's Hospital department of pediatric surgery [5]. The objective of the evaluation was to determine the place and predictors of a successful outcome for conservative treatment in children who have caustic oesophageal strictures. Twenty four children aged between 16 months and 12 years with undilated oesophageal stricture had oesophageal replacement with a peristaltic colonic conduit over a 5-year period, 1986–1990. All strictures followed accidental corrosive burns. The procedure was well tolerated; all the patients were able to swallow within 3 weeks of surgery. There were no operative or postoperative deaths; however, major postoperative complications were threatening pneumothorax (two cases); gastric outlet obstruction due to *Ascaris lumbricoides* (two cases) and cervical fistula (eight cases) which closed spontaneously in each case. Twenty-two patients have been followed up for 2–59 months.

Children tolerate oesophageal replacement well [23]. Endoscopic balloon dilatation has been shown to be a safe, effective, and easy method for the management of oesophageal stricture caused by surgical anastomosis, sclerotherapy and corrosive injury [24]. A total of 136 dilatations were done in 45 patients with an average of 2.6 times/case, range 1–8. The result of dilatation was good in 9 cases, improvement in 18 cases, slight improvement in 15 cases, with only 3 cases showing no response. The follow-up period was 2 years on average (range 0.5–4 years) [24]. Anterograde and retrograde stricture dilatation was performed in 45 children with oesophageal stricture under general anesthesia mainly as an outpatient procedure. Thirty-six children had an oesophageal stricture following tracheo-oesophageal fistula and/or oesophageal atresia repair, and 9 children had severe corrosive stricture of the oesophagus due to lye ingestion. The procedure was well tolerated and effective [25]. The safety and long-term effectiveness of fluoroscopically guided balloon dilatation for corrosive oesophageal stricture was evaluated in 22 patients with a follow-up period of more than one year (range 13 months to 52 months). The average interval between corrosive ingestion and initial balloon dilation was 18 years

(range 2 months to 51 years). Balloons were used and the caliber of the balloon catheter was increased gradually over subsequent dilations, up to a diameter that allowed patients to swallow solid foods. Oesophageal rupture occurred in seven patients and was treated non-operatively in five and surgically in two. Eleven of the 20 could tolerate swallowing most foods [26].

In comparison with other methods this approach was associated with less morbidity and a better anesthetic outcome. The patients started oral intake at one month. Only one patient had minor leakage, and this healed after conservative treatment. The skin patch inserted in the oesophageal wall caused no problem in motility, and the patients could eat smoothly after surgery. A total of 75 oesophageal reconstructions were performed for caustic oesophageal strictures (65 patients) or post-caustic resection (10 patients) at the Naval General Hospital and National Cheng-Rung University Hospital from 1976 to 1991 [27]. Reconstructive procedures included bypass in 61 patients, replacement of the oesophagus through the substernal route in 10, and replacement of the oesophagus through the posterior mediastinum in 4. There were 28 postoperative complications in 24 (32%) of the 75 patients. Cervical anastomotic leakage occurred in 5. Postoperatively, swallow function was considered good in 67 patients (89.3%).

Three hundred and sixty one subjects with corrosive oesophageal injury were analysed derived from 10 retrospective and 3 prospective publications [28]. The cases were divided into those receiving corticosteroids and antibiotics (T) and those that received neither modality (NT) based on inclusion and exclusion criteria. Forty-one percent (41%) of NT cases developed oesophageal stricture and 19% of T cases developed this complication ($p < 0.01$). There were no reported strictures among 72 first-degree oesophageal burns in the combined T and NT cases. The T group contained 54 strictures among 228 patients (24%) with either second or third-degree oesophageal burns. The NT group of 25 patients with the same burn severity suffered 13 strictures (52%) ($p < 0.01$). Reports of death and gastrointestinal hemorrhage did not increase among steroid-treated patients. Corticosteroid therapy may be useful in preventing strictures among patients with second or third degree corrosive oesophageal burns [28].

A metastatic cerebral abscess developed in a 62-year-old female who required repeated dilatation for an oesophageal stricture following accidental ingestion of liquid caustic soda [29]. Unusual problems in oesophageal surgery in childhood include problems seen both frequently, i.e. oesophageal atresia, peptic oesophagitis, and corrosive oesophagitis, and infrequently. This latter group includes conditions as neonatal rupture of the oesophagus, explosive rupture of the oesophagus, achalasia of the cardia, pharyngo-oesophagal fibromatosis, nasogastric intubation stricture and stricture in the immunologically compromised patient [30]. All the above conditions demand diagnosis and appropriate treatment.

Acute consequences of the ingestion of corrosive substances include acute necrosis of the upper gastrointestinal tract, hemorrhage and perforation [31].

It has been reported that endoscopy is a safe, reliable, and accurate diagnostic tool in patients with corrosive ingestion and is also of crucial importance in management and prognosis [32]. A fiber optic intubation was performed in two patients who presented with almost total obliteration of the pharynx, one of whom developed a membrane after corrosive poisoning; in the other, the oropharynx filled with a dense cicatrix in the sclerosing phase of rhinoscleroma [33]. In both patients, a single opening in the membrane provided both a thorough assessment of the pathology and subsequently the passage of a cuffed tracheal tube to secure the airway.

A retrospective study to ascertain the preventive effect of corticosteroids on stricture development was done on corrosive oesophageal burns, over a 12-year period at Adama, Turkey [34]. In 35% of the 235 children diagnosis of the oesophageal burn was confirmed by oesophagoscopy. Children admitted within the first 48 hours received steroid, antibiotic and fluid therapy while fluid and antibiotics were given, if needed, in the rest. Stricture development was found to be statistically significant in late admitted patients versus early admissions.

A patient with a 9-cm stricture of the oesophagus caused by the ingestion of sodium hydroxide was treated by gastric antral patch oesophagoplasty. A full-thickness predicted patch of gastric antrium based on the left gastroepiplotic artery was used to enlarge the oesophageal lumen, thus allowing preservation of oesophageal continuity and utilisation of a functioning lower oesophageal sphincter. The patient ate normally after the operation [34].

It is controversial whether treatment with corticosteroids reduces stricture formation in the oesophagus after the ingestion of caustic material. A prospective study over an 18-year period in which 60 children (medium age 2 years) with oesophageal injury from the ingestion of caustic material were assigned randomly to treatment either with or without corticosteroids. Oesophageal strictures developed in 10 of the 31 children treated with corticosteroids and in 11 of the 29 controls. Four children in the steroid group and seven in the control group eventually required oesophageal replacement. All but one of the 21 children with strictures had severe circumferential burns on initial oesophagoscopy [35]. There appears to be no benefit from the use of steroids to treat children who have ingested a caustic substance. The development of oesophageal stricture was related only to the severity of the corrosive injury.

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Human Toxicology, J. Descotes (Ed.)

C. Pulce and J. Descotes

28. Household products

Accidental poisoning is the most common medical emergency among children and adolescents. Many poisonings occur in the home, especially in the kitchen or the bathroom, where a vast array of potentially toxic substances are kept. Nonfatal poisoning remains a major cause of hospital admissions and emergency room care. For every poisoning death among children under the age of 5, 80,000–90,000 nonfatal cases are seen in emergency rooms and approximately 20,000 children are hospitalized [1].

Between 1985 and 1989, 3,810,405 cases involving children under the age of 6 were reported to poison control centers in the US; 39.4% were associated to pharmaceuticals and 60.6% to nonpharmaceuticals [2]. The agent differed with the age of the child. For those aged between 6 weeks and 17 months, plants were the leading cause (40.0%) but chemicals were the most frequent (25.6%) for those aged between 18 and 35 months and medicines (45.9%) for those aged 36 to 59 months [3]. 30.1% of pediatric ingestions reported to poison control centers involved children with a prior history of poisoning [4] but exposure frequency appears more likely to reflect product availability, the market share of the product and accessibility to the ingestor.

Morbidity is not correlated with the frequency of poisoning. Indeed, many exposures were either nontoxic or minimally toxic. Cosmetics and personal care products, cleaning substances and plants were the most frequently encountered categories (30.4%), yet the hazard factors for the three categories (namely the sum of major effects and deaths divided by the number of reported exposures) were low [2].

Despite preventive measures (child-resistant closures, product reformulation, heightened parental awareness and vigilance) and more sophisticated intervention when poisonings occur, several products still cause pediatric poisoning fatalities [2].

DETERGENTS

The number of softening agents used are legion. Almost all are derivatives of a few straight chain fatty acid radicals. Textiles can be softened by anionic

compounds such as soaps, sulphated and sulphonated oils and tallows, sulphated fatty alcohols, by anionic compounds such as polyoxyethylene emulsions and also by cationic compounds.

Surfactants

Surfactants are one of the major components of detergents and household cleaning products. These synthetic organic chemicals are classified according to the molecular changes required to increase water solubility.

Chemical structures and formulations

Surfactants include [5]:

– *Nonionic surfactants* are saturated or weakly unsaturated hydrocarbon chain substances on which several polar groups are linked, e.g. ethylene or propylene oxides. This group includes electrically neutral medium- to long-chain polyether sulfates, alcohols or sulfonates (e.g. alkylphenoxy-polyethoxyethanols, polyalkaline glycols, fatty acid alkanolamine amides, alkylaryl polyether sulfates, alkyl ethoxylates, polyethylene glycol stearates).

– *Anionic surfactants* comprise saturated or weakly unsaturated hydrocarbon chains to which a hydrophilic group, generally a strong acid such as a sulfate [–O–SO_3] or sulfonate [–SO_3], is linked. The surface-active property resides in negatively charged ions which come from sodium, potassium and ammonium salts of fatty acids, and sulfonated and phosphorylated hydrocarbons (e.g. sodium lauryl sulfate, alkyl sulfate, alkyl phosphate, alkylbenzene and alkyl aryl sulfonates, alkyl ether, alkyl polyethylene–glycol, phenol ether, ester and alkyl ethanolamide sulfates, etc.). These compounds are the most common surfactants in use as commercial detergent products. They promote detergency, wetting and emulsification by lowering surface tension [5].

– *Cationic surfactants* are essentially quaternary ammonia compounds with positively charged surface-active moieties (e.g. benzalkonium, benzethonium, methylbenzethonium, cetylpyridinium, alkyl-dimethyl dichlorobenzene ammonium, dequalinium and phenamylinium chlorides, cetrimonium and cethexonium bromides).

Recommended and current uses

– *Nonionic and anionic surfactants*: these products are currently used for manual dish washing (as liquid or granules), bath and surface cleaners, clothes-washing products and heavy-duty laundry products, non-phosphate granular products, soaps and shampoos [5]. Formulations usually include some but generally not all of the following substances: anionic surfactants, fatty acid amides, nonionic surfactants, sodium tripolyphosphate, orthophosphate, metaphosphate, silicate, sulfate and carbonate, and tetrasodium pyrophosphate. Small quantities of other substances such as protective colloids, corrosion

inhibitors, colouring agents, perfumes may be included, but are likely to change toxicity only slightly, if at all.

– *Cationic surfactants*: Commercially recommended applications include use in disinfectants, industrial and institutional products, fabric softeners, antistatic compounds, and swimming pool and waterbed algicides. Benzalkonium chloride is the most commonly used preservative in ophthalmic medications, solutions for contact lenses and artificial tears [6,7].

Kinetics

Data on detergent kinetics are very few. Isolated studies have been performed, for instance one with alkylpolyethoxylates [8]. Oral administration resulted in the prompt elimination of the ethoxylate portion in the urine, with some appearing in the feces and as CO_2. Lengthening of the alkyl chain increased the fraction of carbon metabolized to CO_2. Radioactivity from labelled alkylpolyethoxylates was absorbed slowly through the skin.

Mechanism(s) of toxicity

– *Non-ionic and anionic surfactants*: the potent irritancy of anionic surfactants can be due to their surface-active properties or ability to denature proteins, including enzymes, but it is likely to be more closely related to their effects on biomembranes. Their adsorptive properties on the surface of the skin are of considerable importance as a primary factor in the initiation of skin roughness [9]. Non-ionic surfactants produce less local irritation than anionics.

– *Cationic surfactants*: inhibition of cholinesterases, various intracellular processes, and a curarizing action on striated muscles have all being suggested to occur [7].

Toxicity

– *Anionic surfactants*: the majority of these products, such as monoalkyl phosphate, exert a remarkably weak irritating effect on human skin in contrast to the high irritancy of commercially used anionic surfactants, like sodium dodecyl sulfate, with the major exception of electric dishwasher products in which builders enhance alkalinity [9]. Aqueous solutions of sodium laurylsulfate produce a mild to moderate (but seldom severe) inflammatory reaction, following prolonged contact. A sufficient inflammatory response can be produced and make the epidermis more permeable to express the sensitization of a topical formulation [10]. Diffusion through the irritated skin or the stratum corneum cannot be excluded, but is always insufficient to account for general symptoms. The ingestion of these products is associated with gastrointestinal irritation resulting in occasional transient nausea, vomiting, diarrhea and abdominal pain.

– *Nonionic surfactants*: As a general trend, a decrease in toxicity is observed in parallel to an increase in chain length. The nonionic surfactants are less toxic and, as would be expected, are no more hazardous than the anionic agents.

– *Cationic surfactants*: Concentrated (10–15%) solutions are caustic and even dilute (0.1–0.5%) solutions produce significant mucosal irritation. Ingestion of large amounts may produce CNS symptoms. Quaternary ammonium compounds, like alkyldimethylbenzyl ammonium chloride, used as algicides for waterbeds have been involved in two cases of poisonings following prolonged oral exposure [7]. There was no irritation of mucous membranes but after 3–4 hours pronounced curare-like symptoms developed rapidly. Symptoms lasted up to 12 hours. Benzalkonium chloride has occasionally been reported as a cause of allergic dermatitis [6]. Similarly, quaternary ammonium compounds used as plant growth regulators induced curare-like paralysis in a patient who had been using one of these products in his greenhouse [7]. Acute accidental poisonings with a hospital disinfectant as a powder to be diluted in water, and containing a mixture of about (15–38%) of quaternary ammonium compounds has been reported [11]. Forty-five mentally disturbed patients accidentally ingested the powder which caused corrosive burns of the mouth, pharynx, oesophagus and in some patients, of the respiratory tract. Thirteen patients died. They all were elderly people. Ten developed inhalation pneumonitis and died of acute respiratory distress one hour to twelve days after ingesting the powder. Progressive deterioration was responsible for the death of the other three between the 19th and 40th day.

Treatment

– *Anionic and nonionic surfactants*: Gastric lavage or induced emesis are obviously contra-indicated. Administration of antiemetics may be useful in some patients. Cutaneous and ocular exposure require water irrigation. Patients may usually be managed at home with symptomatic treatment.

– *Cationic surfactants*: gastric lavage or induced emesis are contra-indicated in poisonings following ingestion of a small amount of concentrated products. The ingestion of water can decrease the severity of the caustic damage caused by powder formulations [11].

Powder detergent adjuvants

These neutral salts, such as sodium sulfate, are used as ballast. Inorganic builders are added to detergents to improve the wetting and emulsifying properties which are inhibited by hard-water minerals, such as calcium: phosphates (usually tripolyphosphates) decrease water hardness by linking calcium and magnesium. Their presence in environmental water may result in sudsing and eutrophication in lakes. Phosphate detergents showed transient irritation of the ocular tissues. Increasing the concentration of non-phosphate builders, especially sodium carbonate or carbonates/metasilicates, results in more irritant formulations. Typical carbonate (non-phosphate) detergent formulations cause considerable ocular irritation followed by opacity and corrosion of the cornea [12]. The extent of eye changes is directly related to the alkalinity of the detergent powders.

Other substances include nitroloacetic acids (nitrilotriacetate), zeoliths (synthetic or natural aluminosilicates: the best known of which is Zeolith A or sodium aluminosilicate [13]), citrates (citric acid); ethylene diamine tetra-acetate (EDTA), a complexing agent of calcium and magnesium, which is poorly biodegradable. The toxicity of Zeoliths is essentially related to their ability to bind heavy metals such as zinc, lead, mercury, cadmium, etc.

Other additives

These include bleaches (perborates, percarbonates, sodium hypochlorite), whitening agents (tetra-acetylethylene diamine), antiredeposal agents (e.g. carboxymethylcelluloses, polycarboxylates), fiber protecting agents (e.g. phosphonates), foam inhibitors (e.g. silicones), enzymes (e.g. proteases, amylases), and optical brighteners (or fluorescent brightening agents).

Optical brighteners are used in the textile industry, as laundry detergents and in cosmetics. The first marketed product was 6–7 dihydroxy-coumarin (esculetin) and the first commercial products were fluorescent derivatives of stilbene (diaminostilbene disulfonic acid derivatives) which have a good affinity for celluloses. Other products such as benzidine, benzimidazole, di-imidazole, and imidazolone derivatives are also in current use. Optical brighteners are not very well known substances but they are present in a great number of common household products. Their physical action, main industrial applications and possible uses in cosmetics have been reported [14]. Toxicological studies showed that optical brighteners may not be very noxious from the viewpoint of acute and short- or long-term toxicity either orally or via contact with the skin and mucous membranes. However, it is of importance to study separately their toxicity considering the diversity of their chemical structure and ubiquity.

Concentrations in household commercial products are very low, accounting for the low toxicity, which does not exclude the risk of contact dermatitis.

– *Colouring substances*: concentrations in household products are very low hence their usually low toxicity which does not exclude contact dermatitis.

– *Perfumes*: concentrations in household products are very low hence their usually low toxicity which does not exclude contact dermatitis.

– *Abrasives*: Pulmonary complications have been observed in workers exposed to the dust of synthetic detergents as well as abrasive soaps. Silicosis-like features have been described following voluntary exposure to silica dust from abrasive soaps. One case of acute silicosis with pulmonary fibrosis due to intentional inhalation of domestic scouring powder rich in silica was described [15] and confirmed by the presence of silicotic crystals within the lung tissue and mediastinal lymph nodes. Another patient with respiratory distress, immunologic disorders and infectious complications with a fatal evolution due to septic shock was recently reported [16].

Liquid detergent solvents

These formulations are similar to detergent granules except that they exist as aqueous or hydro-alcoholic solutions. Alcohol concentrations are too low to cause toxicity except following the ingestion of very large amounts. The toxicity is generally considered to be lower than that of detergent granules, partly because of surfactants granules in the formulation.

Automatic dishwashing detergents

Automatic dishwashing detergents are common household products. They are strongly alkaline and as with every caustic agent, the composition, concentration and physical state of the product combined with the duration of exposure, are the best prognostic indicators of potential toxicity. While the majority of children suffered no serious consequences from the ingestion, it still is possible for devastating sequelae to occur. Kynaston et al. [17] described 18 pediatric cases. Eleven instances of oesophageal injury occurred ranging from mild erythema of the oesophagus to non-circumferential burns of the pharynx, larynx and oesophagus. While a good relationship exists between the symptoms and the presence of oral burns and of more distal lesions as assessed endoscopically, one cannot assume that in the absence of oral lesions, the remainder of the upper gastrointestinal tract will also be normal. Two of five children who had no visible oral burns were found with endoscopic lesions which would have been missed if the clinical evidence had been used alone [17]. Franck et al. [18] reported one case of acute respiratory failure following the accidental ingestion of a dishwashing powder in an 18-month-old infant. The complication due to an oesotracheal edema was increased by the forced intake of water immediately following the caustic ingestion. Endoscopic examination revealed burns of the orolarynx, an oedematous epiglottis and a circumferential third-degree burn of the upper oesophagus.

FABRIC SOFTENERS

Most of the present-day domestic products are dispersants containing about 3–7% of the active cationic softener, and they are normally used in the last rinse of a washing process at the active concentrations of 50 to 100 ppm. A rinsing time of 1–3 minutes at temperatures between 25 and 40°C results in the uptake of 0.1–0.2% of softener by the fibres, based on the weight of the fabric, which is sufficient in most cases to achieve adequate softening. The most obvious properties the cationics confer to fabrics are softness, especially on cellulosic fibers, without giving a limp greasy feel; fluffiness, especially on towels; reduction in friction during ironing and antistatic properties on synthetic fabrics. If required, special types of cationics can be added to the softener to provide germicidal properties. Many commercial materials are complex mixtures rather than single compounds.

The softeners currently on the market are aqueous dispersions and a typical formulation is given in Table 28.1:

Cationic softener	3–7.0%
Rewetting agent (nonionic)	0.2–2.0%
Viscosity additive (Na_2CO_3)	0.1–1.0%
Fluorescent dye	0.05–0.3%
Perfume, coloring, water	up to 100.0%

Table 28.1. *Typical formulation of fabric softeners*

The rewetting agents may be nonionic surfactants or ethoxylated cationics. The viscosity of the final product can be controlled by the addition of short-chain alkyl quaternaries, nonionics, or by electrolytes such as sodium carbonate or acetate.

CLEANERS AND POLISHES

Furniture and floor polishes

These essentially contain hydrocarbon distillates and sometimes mineral seal oil. Kerosene and related petroleum hydrocarbons cause pathologic changes in the central nervous system, leading to neurologic depression and chemical pneumonitis, which may subsequently be complicated by bacterial pneumonia. The oral ingestion of kerosene and other petroleum distillates is potentially more hazardous than the inhalation of vapors. Ingestion is often associated with vomiting which may result in aspiration of the substance into the respiratory tract producing pulmonary damage and edema. The hazards of aspiring hydrocarbons during ingestion depend on viscosity and surface tension, both of which are related to the molecular weight. Hydrocarbons with large molecular weight are more viscous and therefore less toxic. In the presence of aspiration, however, very small quantities may prove fatal, particularly in young children. In fatal cases death usually occurs within 24 hours following ingestion.

Metal and jewel cleaners

The composition of household cleaners is extremely varied from one product to another. The most common component is silica with white spirit associated with various additives. In this case, the risk is solvent-related. Other products include surfactants with their own specific risk. Others include low quantities of acids and can only cause irritation of the digestive tract.

BLEACHES, DISINFECTANTS, STERILIZERS

Household disinfectants

These may contain cationic surfactants and sometimes sodium peroxide, perborate or carbonate, and oxalic acid, or cresol derivates with caustic and general effects (CNS, vascular and nephrotoxic effects). They may also contain sodium dichloroisocyanurate as in sterilizing tablets. Household bleach, "Eau de javel", is an aqueous solution of sodium hypochlorite. Sodium dichromate or hydroxide were added as staining agent, and also as stabilizer. The addition of sodium dichromate has become obsolete in many countries. In France, the concentration of eau de javel is determined by its chlorometric grade (e.g. the amount of chlorine/liter of solution) whereas in most other countries, it is expressed in grams of chlorine/liter of solution. Therefore, 48° chlorometric grade (l chlorine/l solution) = 152 g (g chlorine/l solution); 18° chlorometric grade (l chlorine/l solution) = 57 g (g chlorine/l solution); 12° chlorometric grade (l chlorine/l solution) = 38 g (g chlorine/l solution).

The severity of poisonings following accidental ingestion differs according to the concentration [19]. Products containing less than 5% sodium hypochlorite induce mild to moderate mucosal irritation. Skin, eye and oesophageal irritation depends on the volume ingested, the viscosity, the gastric content, the pH and the duration of contact. Generally, products with a pH below 12.5 do not cause serious burns, but failure to remove moderately alkaline liquids from these areas may produce deep partial-thickness chemical burns, especially after large intentional ingestions. Strong hypochlorite bleaches (15%–20% solutions) may induce caustic injuries and massive suicidal ingestions may produce fatal hyperchloremic metabolic acidosis or aspiration pneumonitis. One case with fatal hypernatremia (185 mmol/l) and neither hypovolemia nor dehydration was reported [20].

The toxic effects on the skin cause reddening with skin damage and severe irritation to the eyes and mucous membranes for concentrated preparations. Some cases of contact dermatitis with positive patch testing have been described [21,22]. Rao [23] reported one death following cutaneous exposure to highly concentrated sodium hypochlorite sold as pool chlorine (10% solution of sodium hypochlorite and excess sodium hydroxide to maintain stability with a pH between 13.2 and 13.5). Toxic effects were extremely severe because of the concentration, and the extended period of chemical exposure (the victim proved to be unable to escape the continuous flow of the toxic solution over his body).

Poisoning by mixture of acidic household products such as toilet bowl cleaners, and sodium hypochlorite is usually due from inhalation of the reaction products. Chlorine gas is sometimes released by some of these mixtures. The accident often occurs in a poorly ventilated, closed space. Chlorine is a highly corrosive gas. Inhalation produces coughing, choking, headache and dizziness. After a latency period of 6 to 8 hours, pulmonary edema with dyspnoea, vertigo, cyanosis and hypotension may occur [24]. However, some of

those exposed may demonstrate long-term persistent obstructive or restrictive pulmonary deficits or increased nonspecific airway reactivity after high-level exposure to chlorine gas. Initial and long-term symptoms following inhalation of mixtures of chlorine-containing cleaners at home are similar but generally less severe than those occurring after occupational exposure [25]. It was suggested that some subjects or certain subpopulations (e.g. smokers) may be more responsive to the effect of chlorine gas and may be at a greater risk of adverse outcome. Bosse [26] reported 86 symptomatic cases of chlorine gas inhalation (of which 73.3% had a domestic exposure). They were treated with nebulized sodium bicarbonate (3 ml of 8.4% sodium bicarbonate mixed with 2 ml of saline) used as a mini nebulizer with oxygen or air. This was repeated as needed and did not preclude the administration of systemic or inhalational bronchodilators. All patients gradually improved, none deteriorated.

In Hong-Kong, Dettol liquid, a household disinfectant which contains 4.8% chloroxylenol, pine oil and isopropyl alcohol, was involved in 10% of hospital admissions related to intentional poisonings [27]. In a retrospective study of 67 cases, serious complications were noted in 8% of cases. Aspiration of Dettol with the gastric content resulted in pneumonia, cardiopulmonary arrest, bronchospasm, acute respiratory distress syndrome, and severe laryngeal oedema with upper airways obstruction.

Sterilizing tablets

These contain sodium dichloroisocyanurate which generates chlorine gas when the tablets are dissolved in water. The solution pH is near neutrality. The mechanism of injury is assumedly the oxidation of proteins, as following the ingestion of liquid chlorine bleaches. Solid caustic agents produce a higher incidence of oesophageal burns than liquids. Siodlak [28] reported two cases of ingestion in children. In the first case, endoscopy showed slough on a swollen right aryepiglottic fold. The vocal cords, trachea, and oesophagus were normal. Endoscopy 6 days later showed normal findings. The second child developed cough, copious vomiting, drowsiness, cyanosis with pronounced stridor. Owing to vomiting, spasm, and local edema, intubation was performed only with extreme difficulty. The supraglottis and hypopharynx were grossly oedematous and ulcerated, precluding extubation for 9 days. Persistent aspiration due to neuromuscular incoordination prevented oral feeding for 8 weeks. He was discharged after three months and subsequently remained well.

A 28-day-old infant who had swallowed one half of a sterilizing tablet presented with a clear nasal discharge, drooling, a swollen tongue, mouth ulcerations, respiratory distress, expiratory rales and signs of pre-shock. Laryngoscopy revealed gross oedema of the nasopharynx and epiglottis whereas the vocal cords and the trachea were normal. Oesophagogastroscopy revealed severe lesions of the oesophagus and stomach. Upper respiratory and pulmonary lesions with atelectasis of the right upper and middle lobes recovered completely after a few days [29].

HOUSEHOLD PRODUCTS FOR CLOTHES

Rust removers

Several products contain hydrofluoric acid or ammonium fluoride. Acute poisonings cause caustic damage of mucous membranes [30]. As the most electronegative element tightly binds cations essential to homeostasis, it may produce, for example, profound hypocalcemia with acute heart failure. Death can result from these processes and also from delayed, explosive hyperkalemia. Therapy of acute poisoning is aimed, first, at preventing the absorption by incorporating the product into insoluble fluoride compounds, secondly, at enhancing fluoride tolerance by maintaining normal blood pH and electrolytes, and at insuring aggressive general support of the intoxicated patient, thirdly, at manipulating renal excretion or removing fluoride with dialysis [31]. When the patient can be supported for 24 hours, the prognosis will improve markedly, although delayed toxicity can occur.

Hydrofluoric acid is frequently used at home as a rust remover and paint remover. Diluted solutions induce progressive and profound tissue damage related to the penetration of fluoride ions [32]. The areas most commonly exposed are the hands and especially the fingers because of handling, and localized digital burns are the commonest toxic symptoms. However, while large-scale dermal exposure can cause death, fatalities following digital exposure are very rare [33]. The conventional methods for the management of burns include local application of 2.5% calcium gluconate gel and the local infiltration of 10% calcium gluconate solution [33]. The tissue irritation caused by the injection of calcium salts and the difficulty in performing injections into the subungual area has prompted attempts at developing other methods of delivering calcium to injured tissues. Regional intra-arterial infusion of 2% calcium gluconate can be the first measure [32,34]. Regional intravenous calcium infusion may also be helpful as it is less invasive and likely to cause fewer complications than intra-arterial infusion. It also involves a lower systemic burden of calcium compared with intra-venous infusion [33]. Intra-arterial infusion of magnesium sulfate is likely to be ineffective based on the results of Cox [35] who compared this treatment with intradermal calcium gluconate in a rabbit model.

Waterproofing compounds

These products are used as sprays and often contain silicones in organic solvents (e.g. 1,1,1-trichlorethane, methylene choride, petroleum derivatives, etc.). Inhalation of large amounts can induce respiratory disorders.

DUST REMOVERS AND ANTISTATICS

Interstitial pneumonia in both lower lobes related to the intensive use of a household dust-away cleansing spray was reported in a 24-year-old woman

[36]. The diagnosis of lipoid pneumonitis was established by bronchoalveolar lavage: macrophages had a great number of vacuoles highly positive to a sudan III dye characteristic of lipids. The spray was composed of 4% mineral oil, 19% aliphatic hydrocarbons, 4% silicon oil, 2% wax, 47.7% water, 0.3% perfume and 22% propellant. The diameter of most spray particles was 40 μ, but less than 10 μ for 10% of them.

Recreational sniffing of antistatic aerosols used for dust removal in electronic and hifi-video equipment was recently noted by French poison control centres [37]. These aerosols contain either fluorocarbons or mixtures of fluorocarbons and hydrochloroflurocarbons. Recreational use is intended to induce transient alterations of the voice after spraying the aerosol in the mouth. Although reported symptoms were mild in most instances, malaise, transient loss of consciousness and even convulsions have been described.

Fitzgerald [38] reported one death due to the recreational use of chlorodifluoromethane and chloropentafluoroethane with postmortem blood concentrations of 71 mg/l and 0.30 mg/l, respectively. The patient was found coughing and wheezing at home, and he presented with ventricular fibrillation at the time of hospital admission. A similar case was reported in a 15-year-old boy after intentional inhalation of an automobile air conditioner recharge unit containing dichlorodifluoromethane [39].

DEODORIZERS

The composition of deodorizers is relatively heterogenous. Some contain citronella oil which is also used as an insect repellant and in perfumery. Few poisonings have been reported, due to its powerful odour. Mant [40] had reported a 21-month-old female child who drank about three teaspoons of a preparation containing citronella oil. The child began to vomit at once and the smell of citronella was apparent. Salt and water as emetics were administered which caused further vomiting. One hour post-ingestion the child was admitted to the hospital; very shocked, pulseless and retching continuously. She was lavaged and treated symptomatically. Despite the administration of adrenaline and nikethamide, she became cyanosed, had convulsions, vomiting blood-stained fluid, and died 5 hours post-ingestion. It is questionable whether the fatal outcome was solely due to the toxicity of citronella oil but it is suggested that the human toxicity of citronella oil may need to be reevaluated.

Temple et al. [41] reported five patients among whom two were managed by observation only, as no lavage was performed because the two had ingested an unknown amount which finally resulted in no untoward effects. In the three additional patients, gastric lavage or vomiting was performed. In one patient, gastric lavage may have produced aspiration pneumonia. In another patient, the prominence of hilar markings and an exaggerated peribronchial marking in the right lobe were shown by chest X-ray. In the third patient, the physical examination was normal apart from oral irritation and a strong odor of citronella. Although the management of ingestions of essential oils such as eucalyp-

tus, turpentine and penny oil has usually been aggressive [41], it is increasingly questioned whether these measures are adequate in citronella oil poisonings. No digestive decontamination is probably ever justified.

IGNITION SOURCES, MATCHES

Matches have nearly lived down their reputation for toxicity. At one time, the principal components of matches were white (yellow) phosphorus, potassium chlorate, and sulfur, and they were a cause of marked toxicity [42]. The legislation of many countries prohibits the use of white phosphorus in matches so that it has been replaced by red phosphorus or phosphorus sesquisulfide. Red phosphorus is relatively non-toxic unless it contains the white form as impurity. Other ingredients formerly used such as potassium chlorate and bichromate, magnesium sesquisulfide, zinc oxide, abrasive and glue. The accidental ingestion of matches often occurs in children and usually has no serious effects. Only 2% of reported cases experienced trivial digestive disorders.

Two toxic products are present in match-heads used in France: potassium chlorate and dichromate. Potassium chlorate estimated lethal dose ranges between 1 g in infants and 5 g in older children, but it seems that toxic effects are cumulative because of the slow excretion of the chlorate ion and repeated 1 g ingestions have been fatal. Adult oral potassium bichromate lethal dose ranges between 500 and 1000 mg and toxic doses between 100 and 200 mg.

Recently, a 3-year-old boy ingested 40 match-heads, corresponding to approximately 500 mg potassium chlorate and 5 mg potassium dichromate. He developed acute renal failure requiring dialysis, and completely recovered. Hemolysis and/or methemoglobinemia has not been documented in this case [43].

OFFICE MATERIALS

Glue

Adhesives contain resins dissolved in various solvents. Most household glues have a low toxicity. One case of accidental administration of a cyanoacrylate-containing adhesive into the eye was reported by Vrabec et al. [44]. The 13-year-old boy immediately experienced a sensation of pain and an inability to open his eye. The eye was flushed with saline and on examination it was found to sealed close. After removal of the polymerized glue, the eye showed a moderately injected conjunctiva, superficial punctuate keratitis with no epithelial defects, and a normal anterior chamber.

Penmarkers

Most penmarkers are not toxic. Markers for whiteboards may contain solvents such as toluene, xylene, ketones, alcohols, acetates, etc. Most are odorous

and can induce nausea and headache, but quantities are too low to induce other symptoms.

Correction fluids

These are used to blank out typing errors and are commonly sold as 10-ml bottles of white opaque liquid with an application brush. Ong et al. [45] reported the results of their study of 20 brands of correction fluids widely used among school children in Indonesia, Malaysia, and Singapore. The most common component was 1,1,1-trichloroethane. Carbon tetrachloride, N-hexane, methylene chloride, and methylcyclohexane were also detected in significant amounts. Two of the analysed correction fluids were found to contain high levels (approximately 50%) of carbon tetrachloride; one specimen contained 10% of trichlorethylene and four concentrations of methylene chloride greater than 20%. Another major component was N-hexane and five specimens contained concentrations greater than 50%.

REMOVERS

Cloth removers

The composition of these depends on the intended use, for instance dye or ink removers, oil or grease removers, rust removers. Some, principally oil or grease removers, contain hydrocarbons with few molecules and low-molecular-weight alkanes and cyclanes with 5 to 7 carbons. Ingestions induce changes in the central nervous system resulting in neurologic depression and chemical pneumonitis, which may subsequently be complicated by bacterial pneumonia. Fatal cases have been described [46].

Glue and nail polish removers

Fogh and Wickstrom [47] reported five cases of poisoning with gamma-butyrolactone used as glue removers especially for cyanoacrylate glue and also in nail polish removers. All children ingested only a few ml and presented a quite rapid unconsciousness and at least in one case respiratory depression. All children recovered. Durak et al. [48] reported one additional case due to the accidental ingestion of a few ml of a gamma-butyrolactone-containing nail polish remover. The accidental ingestion of an artificial fingernail remover containing 100% nitroethane resulted in life-threatening methemoglobinemia in a 20-month-old child [49]. Geller et al. [50] described a 3-year-old child who presented, three hours after ingesting an estimated 15 to 30 ml of artificial nail remover containing 95% acetonitrile, mental status abnormalities and vomiting, prior to generalized seizure, despite prompt (30 minutes) gastric lavage and charcoal administration. The administration of sodium thiosulfate was

associated with uneventful recovery. Losek et al. [51] reported a similar case in a 23-month-old child after the ingestion of approximately 60 ml of a nail remover containing 98% to 100% acetonitrile. Vomiting appeared 6 hours later. At twenty-four hours post-ingestion, he began having staring episodes and was not responding to his mother. Blood lactic acid levels decreased from 50.1 mg/dl to 14.2 mg/dl after two intravenous injections of sodium thiosulfate. Whole blood cyanide levels were 2.1 μg/ml and 3.8 μg/ml, 12 hours and 25 hours post-ingestion respectively.

Paint removers

Furniture stripping has become an increasingly popular hobby over the past several years, so the potential for toxic exposure increases. Methylene chloride is a major ingredient of paint and varnish removers and has been reported to cause central nervous system depression, carbon monoxide poisoning and sometime pulmonary injury. Buie et al. [52] reported the case of a 34-year-old man who had been stripping furniture for the previous four days in a poorly ventilated area and who developed severe respiratory insufficiency with pulmonary edema and bilateral pleural effusions requiring assisted ventilation. This case was unusual in the degree of pulmonary damage that occurred.

Graffiti removers

They contain formic, fluorhydric, chloroacetic acids, mineral bases (caustic soda, potash), oxidising agents (polychloroisocyanurate, sodium hypochlorite, hydrogen peroxide), solvents (petroleum and aliphatic chlorinated hydrocarbons, chlorobenzene, ketones, alcohols and glycols, phenols, dimethylformamide, hydrofurans). Most have a cutaneous toxicity, some respiratory, neurologic, renal or liver toxicity [53]. The exact formulation of each product must be checked to determine the exact toxicity.

HOUSEHOLD PESTICIDES

Nearly all families use some form of pesticides in or around the home. Forms of commercial products are heterogenous: spray can, liquid spray, strip, dust, shampoo, etc. These products have different uses, e.g. as insect repellents, for pets, and so on. Several household insecticides contain organophosphates such as malathion or dichlorvos, carbamates such as propoxur, organochlorates; but most of them are now made from synthetic pyrethrinoids.

Markowitz [54] reported the case of an urban family who had an excessive exposure to organophosphate and carbamate pesticides. They used commercial pesticide application for extermination of fleas. They had used unknown pesticides two times several weeks previously. Later, a professional applicator sprayed an unknown pesticide using a tank and hose apparatus. He sub-

sequently used eight pressurized canisters filled with a commercial product containing two active pesticidal ingredient: an organophosphate (dichlorvos) and a carbamate pesticide (propoxur). Each container was recommended to be used for 6000 cubic feet and the apartment was estimated to have a volume of 7000 cubic feet. All three family members developed symptoms compatible with cholinesterase inhibition, namely headache, lightheadedness, wheezing, shortness of breath, nausea and fatigue. Serial measurement of red blood cell counts and serum cholinesterases soon after exposure and during several months confirmed the diagnosis of pesticide poisoning. This report demonstrates that misapplication of pesticides commonly used in residences of urban areas can cause acute pesticide poisoning and shows the value of repeated measurements of cholinesterases during the post-exposure period in establishing the correct diagnosis.

BUTTON BATTERIES

Miniature disc batteries are commonly found at home and are easily ingested by small children. The most widely used are alkaline manganese, mercury and silver batteries. All contain alkalis in sufficient concentration to cause caustic injuries even though the electric effect of the battery should also be considered. The majority of children who ingested a button battery have remained asymptomatic and passed the battery per anum within two to seven days, although button battery passage may take as long as 14 days or even more [55,56]. Exceptionally, if an ingested disc battery remains in the oesophagus, it can be corroded and release its toxic contents. The concentrated potassium and sodium hydroxides may cause liquefaction necrosis. In the very rare event of its lodging in meckel's diverticulum, it might result in perforation [55]. Normally, children with battery lodgement in the oesophagus typically present with refusal to take fluids, increased salivation (often with black globules in the saliva), dysphagia, vomiting, and sometimes hematemesis, fever. One child with a battery lodged in a meckel's diverticulum complained of intermittent abdominal pain and exhibited guarding, tenderness, and protracted vomiting [57].

Litovitz et al. [55] published a large series of battery ingestions. Most cases followed a benign course as only 2 of 2382 (0.08%) cases in this series demonstrated a major effect. As previously reported, both patients with a severe outcome had batteries located in the oesophagus. Symptoms occurred in 9.9% of patients in this series, and most of them were related to the gastrointestinal tract. Twenty-eight patients had rashes, possibly in relation with nickel hypersensitivity. Mercury toxicity was not in evidence; although 565 batteries were estimated to be mercuric, no symptoms of mercury poisoning became apparent. Although analytic screening was limited to patients with split or nearly split batteries, only one patient demonstrated an elevation in mercury levels, and this child did not require chelation or develop clinical evidence of mercury poisoning.

So ingested batteries should not be regarded as inert foreign bodies and be removed only if they become lodged or show signs of damage on radiography. In these rare cases, emergency endoscopic removal is still the only relatively safe and effective treatment [57]. The incidence of untoward outcome from battery ingestion was very low and 7 cases of miniature button battery impaction in the nose have been reported by Tong et al. [58]. The complications included septal burns in five patients leading to septal perforation in one child, one case of severe nasal bleeding and one case of necrosis of the lateral nasal wall. This report underlines the potential hazards of button batteries as foreign bodies in the nose and emphasizes the need for rapid removal and long term follow-up of these patients.

TASTE AVERSIVE AGENTS

Denatonium benzoate (Bitrex®) has been used in the United States for over 20 years as an alcohol denaturant. In recent years, it has been heavily promoted for inclusion in household products, gardening products, and cosmetics to prevent accidental ingestions by children. A concentrated solution of denatonium benzoate which would be sold directly to the public for addition to household products is available in USA. The efficacy and safety studies on denatonium benzoate are limited and may be subject to varying interpretations when viewed in the context of a potential poisoning situation. Safety data indicate a low toxicity profile. However, there are significant gaps in knowledge, especially relating to chronic toxicity in humans, teratogenicity, and human hypersensitivity potential [59]. A 33-year-old man developed asthma and urticaria from exposure to denatonium benzoate in an insecticidal spray. He had previously developed the same symptoms following exposure to an alcohol-based skin disinfectant and other products denatured with denatonium benzoate. The cause of his symptoms was thus likely to be an immunologic mechanism of the immediate hypersensitivity-type. Currently available, admittedly limited data indicate that denatonium benzoate may actually have a low toxicity profile. Considering its wide availability as a denaturant for alcohol, it is surprising that human toxicity has been reported only once. However, denatonium toxicity may have been unrecognized because it is usually not included on product-ingredient lists since it represents a small percentage of the total chemical make-up of the product. No data exist on acute ocular or inhalation exposure in humans, chronic skin exposure in humans or animals, or chronic inhalation exposure in humans or animals. Its safety on broken or abraded skin has not been investigated. There are no teratogenicity studies.

In July 1991, The American Academy of Veterinary and Comparative Toxicology passed a resolution to encourage the use of a bittering agent to limit the ingestion of hazardous materials by companion animals [60]. Rodgers [61] expressed the view that some of the products, such as caustics and hydrocar-

bons, to which aversive agents might be added may produce toxicity with a single swallowing and it is unlikely that the addition of an adversive agent would have a beneficial effect on the outcome of such ingestions. He suggested that addition of denatonium benzoate might actually increase the potential for toxicity of such ingestions because vomiting might increase the risk of aspiration. He therefore recommended the use of denatonium benzoate in a limited number of products including those containing ethylene glycol, methanol and toxic pesticides.

In summary, denatonium benzoate appears to be safe when used at low concentrations as an aversive agent. However, there are limited data about whether aversive agents have an impact on either the number or the severity of pediatric ingestions, and its use should not be a substitute for other preventive measures such as child-resistant closures.

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29. Food-borne poisonings

INTRODUCTION

Food and water may be contaminated by various sources including bacteria, toxins, viruses, parasites, animal tissues, plants, algae, molds and chemicals. For this reason, food-borne poisoning still represents a serious public health problem. However, it is difficult to draw a precise picture of the situation for various reasons: data recording varies from country to country; under-reporting is the rule; the etiological factors are not always easy to identify because of the incubation period and the non specificity of the symptoms; and the overall situation is quite different in developed and developing countries. For example, the American Association of Poison Control Centers reported 46,482 exposures in 1991, with only one death [1]. However, Bishai et al. [2] using different sources of information, evaluated at 12.6 million the number of cases per year in the United States.

In developed countries, even though the morbidity and the mortality from food poisonings have seemed to decrease in the last decades, new problems are emerging due to rapid urbanisation; large-scale food production, distribution and retailing; changes in behaviour and the occurrence of hypersensitive groups (for example, AIDS patients or organ-transplant patients) [3–5]. While traditional food pathogens were progressively controlled by better sanitation and personal hygiene, good manufacturing practice and, more recently, Hazard Analysis Critical Control Points (HACCP) regulations [6], new problems have emerged. The pathogens involved are especially *Campylobacter*, *Salmonella enteritides*, enterohemorrhagic *Escherichia coli* and *Listeria monocytogenes* [7,8].

In developing countries, food-borne poisoning is still a source of high morbidity and mortality because of poor sanitation and personal hygiene, lack of availability of uncontaminated water, artisanal food production, transformation and distribution, hot climates and lack of refrigeration facilities, malnourishment especially in young children and inadequate medical facilities. For example, a study by Ferreccio et al. [9] in Chile showed that in a low socio-economic area of Santiago, a child had a 67% chance of experiencing shigellosis in the first 5 years of his life. Similar situations are experienced in other parts of

the world. In the International Center for Diarrhoeal Disease Research in Bangladesh, Baqui et al. [10] were able to study 2635 patients in one year which represent only 20% of all admissions. Similar large studies have been done in Nigeria [11], Hong Kong [12], Thailand [13], Brazil [14] and many other countries.

Travelling has also been a cause of exposure to unfamiliar pathogens, different food habits, different hygiene standards and spread of contagion [15–17]. New approaches and techniques are being developed and implemented in order to improve our knowledge of the situation, to define more precisely the origin and the spread of the outbreaks, and to measure the biological properties of the involved pathogens in order to increase our efficiency in the prevention and treatment of these diseases [3,8,18–20].

It is beyond the scope of this chapter to cover all sources of food poisonings. Many of the subjects are covered in other chapters of this book (plants, mushrooms, pesticides, heavy metals, organo-chlorinated products).

BACTERIAL SOURCES

Bacterial infections

Bacteria pathogenic for humans may be ingested with food or water, and invade the intestinal mucosa where they may multiply or pass to other organs. These food infections are generally characterized by a long incubation period (days) and a relatively large dose of pathogens required to produce a disease [21].

Shigella. This bacteria is still a major factor of morbidity and mortality in developing countries, especially among malnourished children [10,22–25]. International travelling increases the risk of contracting this disease [26]. This type of infection is relatively rare in developed countries [27]. However, Israel has been an exception to that rule especially because of water contamination [28–31]. It is characterized by an incubation period ranging from 1 to 7 days, followed by abdominal pain, diarrhoea and fever. The watery stools often contain blood, mucus or pus. Prognostic indicators such as persistent diarrhoea, intestinal obstruction and encephalopathy should be taken into consideration [32–34]. Molecular epidemiologic techniques have increased our capacity to survey the outbreaks [21,35,36]. Resistance to many antibiotics has developed in many strains, making the choice of an appropriate treatment protocol more complex [37–40]. Breast-feeding is still considered an important measure of protection for young children [41–43]. The control of houseflies is also an important preventive measure [44]. Because of the prevalence of the disease and its high morbidity ratio, the development of efficient vaccines is still an important objective [45].

Salmonella. The situation of the salmonella infections differs considerably between developing and developed countries [7]. In developing countries, *Sal-*

monella typhi or *paratyphi* are most prominent. These bacteria are host adapted to man and highly invasive. They will penetrate the intestinal mucosa and pass into the lymphatics producing a systemic infection with high fever and diarrhoea only late in the disease. In developed countries, *Salmonella typhimurium* and *Salmonella enteritis* are most frequently involved. After an incubation of 12–36 hours, the bacterias release an enterotoxin in the small bowel, producing diarrhoea which may contain blood or mucus. There may also be mild fever, headache, chills and prostration for 2–5 days.

Many outbreaks have been recently described in Britain, France, USA and Canada [46–50]. In many instances, theses outbreaks were related to the consumption of raw egg shells or egg products [51–54]. The study of the phage types helps in the identification of the source and the extent of the dissemination [55]. A dose–response study illustrates how the ingested dose is an important determinant of the incubation period and the severity of the acute disease [56]. Typhoid fever is a much more severe disease. After an incubation of about one week, the bacteria proliferate in the lymphoid tissue and lymph nodes and then pass into the blood. Fever, headache, malaise, abdominal pain, muscle aches, nausea, anorexia, cough, sore-throat, and moderate diarrhoea then occur. Localised infections in other tissues and organs may follow. Neuropsychiatric symptoms may also be seen.

Campylobacter. There are two main species of Campylobacter likely to cause human infections, *Campylobacter jejuni* and *C. coli*. Both may produce either a mild and brief attack of diarrhoea or a more severe disease with watery or bloody diarrhoea after an incubation period of 1 to 8 days. Fever, malaise, abdominal pain and headaches will also occur. Many outbreaks have occurred in recent years both in developing [57–62] or developed countries [63–70]. These outbreaks are more prevalent in patients with a deficient immune system [71]. Campylobacteriosis is also a significant zoonotic disease [72,73]. The most dangerous complication of campylobacter infection is the Guillain-Barré syndrome [7], but it may also produce various neurological complications. It also plays a role in a large proportion of patients suffering from gastritis or gastric ulcers.

Listeria. Until about 10 years ago, listeriosis was considered to be a zoonotic disease. Since then, it has become clear that food could be a significant cause of poisoning. Even though there are many listeria, only *Listeria monocytogenes* is capable of affecting man. The two target populations are pregnant women and vulnerable individuals, namely very young children, elderly patients and patients with a compromised immune system. If contaminated during her pregnancy, the woman may develop a mild clinical syndrome (flu-like syndrome). However, her pregnancy may be complicated by abortion, or delivery of a stillborn or premature child with neonatal listeriosis. Excellent reviews have been published recently [7,74–76]. Since the knowledge of the problem is relatively new, methods for the identification of the dietary risk factors, the virulence factors, the infective dose, the methods of control of the food industries, and the detection methods are still under development [74,77,78].

Food-borne bacterial intoxications

In this situation, the toxins are produced in the food by the bacterias before ingestion. The dose required to cause poisoning is small and the delay between ingestion and the development of symptoms is short (a few minutes to a few hours).

Staphylocci. Staphyloccal intoxication is extremely common throughout the world. Certain strains of *Staphylococcus aureus* are capable of producing one or more enterotoxins as they multiply in some favourable food environment. Man is the main reservoir of the bacteria and his nose is the principal source of food contamination. Infections of the skin in food handlers are also important sources of contamination. Bacteria can grow rapidly under optimal conditions. Enterotoxins (types A to E) which may then be produced will not be destroyed by cooking or pasteurization. Even though the prevalence of this type of intoxication is still high, the pattern is changing in many countries. For example, in the U.S.A. between 1977 and 1981 more than 7000 persons suffered from staphylococcal intoxications and enterotoxin A was the only toxin incriminated [79]. Raw food of animal origin was identified as an important source of poisoning [80]. In the U.K. a survey of 359 outbreaks between 1968 and 1990 involved enterotoxin A in 79% of cases [81]. The ever-changing, recurring aspects of this public health problem along with its diversified origins remains a challenge for effective prevention programs [82–86].

Botulism. Even though the occurrence of botulism is rare, it remains a dreadful disease because of its high mortality rate. The involved bacteria, *Clostridium botulinum* is a gram positive rod that produces a heat-stable spore. The heat-labile neurotoxins are considered to be the most potent natural poison in the world [87]. There are three main forms of the disease: food-borne botulism; infant botulism; wound botulism. Periodic outbreaks occur in various parts of the world involving mainly type A and E but occasionally, type B [88–104]. In the case of infant botulism, the toxin is formed in the intestinal tract after ingestion of contaminated food [105–108]. Infant botulism was also described in adults [109–111]. Wound botulism is quite a rare phenomenon and occurs when a wound becomes contaminated by the pathogen [112].

Clinical symptoms occur generally 12 to 36 hours after ingestion. Nausea, sore throat, dry mouth, weakness and difficulty in speaking are observed. After 3 to 7 days, the cranial nerves become affected (blurred vision, diplopia, dysarthria and dysphagia). Fixed, dilated pupils may be seen. Respiratory failure is the general cause of death. The trivalent antitoxin (ABE) is used in most cases.

Bacillus cereus. This bacteria is a gram positive, spore-forming rod. Poisoning generally occurs following the ingestion of rice-based dishes. It is capable of producing 2 different toxins. First, an emetic toxin which induces an acute attack of nausea and vomiting, a few minutes to a few hours after ingestion. The disease is difficult to distinguish from staphylococcal intoxications. The second toxin is an enterotoxin. In this case, the incubation time is

between 8 an 16 hours. The disease is characterized by abdominal pain, watery diarrhoea and nausea. The treatment in both cases is symptomatic. More recently, it has been involved as a cause of serious non-gastrointestinal infections. These infections may be quite resistant to many antibiotics [113]. Occasional outbreaks almost always involve inadequate conservation of food before eating [114–119].

Scombroid poisoning. This type of poisoning occurs after ingestion of scombroid fishes, like tuna and mackerel, that have undergone partial microbial decomposition. The clinical picture occurs from a few minutes to about 2 hours after ingestion and mimics a histamine reaction with flushing, headache, palpitations, dryness of the mouth, nausea, vomiting, abdominal pain, diarrhoea, urticarial reaction, sensation of thirst and difficulty in swallowing. Although histamine plays a significant role in the pathogenesis of scombroid poisoning, it should not be confused with an allergic reaction [120]. Other fishes may be concerned beside the tuna, bonito, skipjack, mackerel and mahi-mahi [121]. Non-commercial and recreational fishing may also be involved in such cases and, most of the time, will go unreported [122]. The origin of the histamine or other amines responsible for the clinical syndrome is still debated. Some consider that endogenous histamine released by mast cell degranulation has a significant role in the etiology of scombrotoxicosis [123], but others consider that histamine is most likely to originate from the spoiled fish [124]. Finally, the hypothesis has also been raised that saxitoxin-like substances may play a role in scombrotoxicosis [125].

Bacterial toxi-infections

In these situations, the ingestion of bacteria and their multiplication in the intestines will entail the production and release of enterotoxins.

Cholera. This toxi-infection is caused by an aerobic, slightly curved gram-negative rod with a single flagellum. Man is the only natural reservoir and contamination generally occurs through ingestion of water, fishes or shellfish in areas where poor hygiene and low socioeconomic status predominate. Many endemics and epidemics have occurred in the past but the Western Hemisphere seemed to be free of that risk until 1991 [126–128]. The disease may be caused either by *Vibrio cholerae proper* or the *Vibrio cholerae el tor* sub-type. A new toxigenic vibrio cholerae 0139 strain was recently described in southern Asia and imported into the United States [129]. Even contaminated municipal water seems to be involved occasionally [130]. The incubation period varies between 1 to 5 days. Abrupt onset of vomiting without nausea is generally the first sign. It is followed by an explosive, painless diarrhoea. Rice-water stools are rich in potassium and bicarbonate ions and may produce a loss of 1 liter of fluid per hour in the acute phase. If dehydration is controlled, the disease is self-limited. The strain of *Vibrio cholerae* involved in the South American epidemic also showed multi-drug resistance [127]. Other affected areas in the world in recent years include Angola [131], Bénin [132], Burundi and Zimbabwe [128] and

Nigeria [133]. However, it is still a frequent cause of diarrhoea in some Asian countries. Guidelines for clinicians and nurses have been published recently since most health professionals of the western hemisphere have never encountered this disease [134–136]. This new epidemic also stimulated a lot of research activities in the areas of prevention and management of the disease [137–139].

Enterotoxigenic *Escherichia coli*. *Escherichia coli* is a small aerobic gram-negative rod either motile by a flagella or non-motile. Most strains are harmless commensals but some may invade the intestinal mucosa while others produce enterotoxins. The most frequently involved strain is the enterotoxigenic *E. coli*. It possesses a heat-stable (ST) and a heat-labile (LT) (cholera-like) toxins. It is a frequent cause of the traveller's diarrhoea [15]. A second strain, the infantile enteropathogenic *E. coli* is a frequent cause of diarrhoea in children. The third strain, the enteroinvasive *E. coli* causes a shigellose-like clinical picture. Finally, in 1982, following an outbreak of an unusual gastrointestinal illness, a new pathogen was identified: *Escherichia coli* 0157:H7. This bacteria is generally responsible for a severe illness including three different syndromes: hemorrhagic colitis, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura [140–142]. Most North American outbreaks involved the ingestion of hamburger meat [143]. The severity of the disease caused by this strain of *E. coli* is related to the production of shiga-like verotoxin [144,145].

Clostridium perfringens. This encapsulated anaerobic gram-positive bacillus readily forms spores when it is growing in the intestinal tract. It will then produce four major lethal toxins (*Clostridium perfringens* type A to E). Poultry, cooked meat, beans and spices are frequently involved in outbreaks [146–149]. The incubation period varies between 6 to 24 hours. Then, nausea with watery diarrhoea occurs and last for about 24 hours. Vomiting, fever and severe abdominal pain are exceptional. Multiple typing techniques are useful tools in the epidemiological surveys of these outbreaks [150].

Vibrio parahemolyticus. This is a common disease in Japan where fish and shellfish may become contaminated in their marine environment. The ingestion of raw fish or shellfish especially during summer months may produce abdominal pain with watery diarrhoea. It may also occur occasionally in other parts of the world [133]. The incubation period varies considerably (from hours to days) and is followed by painless, watery diarrhoea. Only supportive treatment is required.

POISONINGS FROM ANIMAL TISSUES

Ciguatera

This disease is caused by the ingestion of reef fish contaminated by ciguatoxin and other toxins (maitotoxin, scaritoxin and possibly palytoxin and

okadaic acid). These toxins are produced mainly by the dinoflagellate *Gambierdiscus toxicus* but perhaps also by other dinoflagellates. Herbivore fishes along with piscivore species may contain the toxins and produce the disease in man. Ciguatoxin is a sodium channel agonist, producing an increased concentration of intracellular calcium. This will increase the force of muscle contraction. The clinical picture include gastrointestinal, neurological and cardiovascular signs and symptoms. Many pharmacological agents have been promoted for the treatment of this syndrome, mannitol IV being at present evaluated by many research groups. This type of poisoning has been the subject of extensive recent reviews [151–153]. Various aspects of the clinical response have also been studied (disturbance of temperature perception, orthostatic hypotension, repeated exposures, dose response) [154–158].

Shellfish poisoning

Various illnesses have been described following the ingestion of contaminated shellfish [159,160]. They occur when the shellfish filter feeds on toxin producing dinoflagellates. The shellfish are not affected by these toxins but they accumulate them in their flesh. Different species of dinoflagellates are responsible for the occurrence of three main types of poisoning:

Paralytic shellfish poisoning is caused by *Protogonyaulax catenella* and *P. tamarensis*. The clinical picture including nausea, vomiting, peri-oral numbness and lightheadedness occurs rapidly after the meal. Within very few hours, muscular palsy may progress to respiratory arrest and death. Treatment is symptomatic [161–163].

Neurotoxic shellfish poisoning is produced by the toxins of the dinoflagellate *Ptychodiscus brevis*. The neurotoxin is irritating to mucous membranes and skin when individuals come in contact with the so-called red tide. A few hours after ingestion of contaminated shellfish, gastrointestinal (nausea, vomiting, abdominal pain, diarrhoea) and neurological (paresthesia, temperature reversal, myalgia, vertigo, ataxia, weakness) symptoms develop. The clinical picture is quite similar to ciguatera poisoning [164].

Domoic acid poisoning was first described in Japan from the red alga *Chondria armata*. In 1987, an outbreak of 145 cases occurred in Canada. The clinical picture was characterized by nausea and vomiting followed by a complex neurological syndrome. Confusion, weakness, sleepiness, abnormal behaviour, memory problems, difficulty to concentrate and, sometimes, convulsions may occur. Permanent neurological sequelae may follow [165–167].

MYCOTOXINS

Different mycotoxins may be produced naturally from molds. Food contaminated by these mycotoxins have been known for more than a century to produce human poisonings [87]. This subject is too complex to be covered in this chapter.

One of these mycotoxins however, has raised a lot of scientific and public health interest mainly because of its carcinogenic properties. Aflatoxin has been the subject of extensive literature reviews [168–170].

VIRUSES

Hepatitis A, rotavirus and small round structured viruses (SRSV) are examples of food-borne viral infections that are more prevalent in developing countries with low hygienic standards but that may also occur occasionally in developed countries [171–173]. Rotavirus is more frequently involved in infant's diarrhoea. In adults, the Norwalk strain predominates. Enteric adenoviruses have also been involved in various outbreaks.

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Human Toxicology, J. Descotes (Ed.)

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30. Mushrooms

Mushrooms are very common in many parts of the world. Although many of them are edible and tasty, others may cause severe poisonings: over 5000 species have been identified, of which approximately one hundred are toxic and only a few potentially lethal. In most instances, mushroom poisonings are accidental; poisonous mushrooms are mixed with edible mushrooms by amateur collectors which results in acute poisonings of varied severity. Suicidal ingestion of mushrooms is uncommon but has been reported. Mushrooms containing psychotropic substances are sometimes ingested for addictive purposes [1]. The intravenous injection of extracts from these mushrooms has been described [2].

Mushroom poisonings are relatively common but seldom severe. A survey of the American Association of Poison Control Centers found that 0.6% of all inquiries received by Poison Control Centers in the US in 1989 involved mushrooms and that only 3 fatalities (caused by *Amanita phalloides*) were observed among the 9,208 inquiries about mushroom poisonings [3]. Similarly, 0.4% of all inquiries received in 1987–1992 by the Poison Information Centre in Berlin (Germany) involved mushrooms poisonings, with three fatalities due to *Amanita phalloides* [4].

GENERAL PRINCIPLES OF MUSHROOM POISONINGS

The diagnosis of mushroom poisoning is not easy. It can be based on several criteria [4]:

– The development of clinical symptoms following the ingestion of mushrooms. In most instances, mushroom poisonings are associated with gastrointestinal disturbances of either rapid or late onset. More typical symptoms, such as neurological signs, may develop and give clues on the offending species.

– The development of similar symptoms in a cluster of individuals who shared the same meal is important evidence even though the symptomatology may greatly vary, depending on the amount ingested and the individual susceptibility.

– The identification of the ingested mushrooms will ideally confirm the diagnosis. However, it is extremely difficult to obtain an accurate and reliable

identification [5]. Morphological characteristics, such as annulus, spores, vulva, lamellae, may be useful, but mycologists with a good identification know-how are seldom found. In addition, it may be impossible to obtain remains of eaten mushrooms and even then they may no provide useful information. Analytical methods have been designed to identify mushroom toxins and even though they can sometimes be very sensitive, these assays are not routinely available in most clinical centers. It is therefore no surprise that in the recent survey by the American Association of Poison Control Centers [3], mushrooms were identified in only 313 out of 9208 cases.

The diagnosis of mushroom poisonings is thus often uncertain. The management of patients is therefore all too often based on the severity of clinical symptoms, their delay of onset, and observed changes in laboratory parameters, for example increased liver enzymes.

Associations of clinical symptoms may present with some specificities so that mushroom poisonings are quite often grouped according to clinical syndromes instead of the offending mushrooms. In this regard, the delay of symptom onset is a very critical prognosis factor to be considered, as mushroom poisonings with a short delay, which account for more than 90% of mushroom poisonings in France, are usually mild to moderate whereas severe poisonings have a delayed onset in the vast majority of cases [6].

MUSHROOM POISONINGS WITH A SHORT ONSET

Even edible mushrooms may cause gastrointestinal disturbances when excessive amounts are ingested. Indeed, many species contain trehalose which may cause abdominal pain and diarrhoea, particularly in those individuals who lack the gut enzyme trehalase. Symptoms typically occur 15 minutes to 2 hours after ingesting the mushrooms and include nausea, vomiting, diarrhoea, and abdominal pain. This gastrointestinal syndrome is usually self-limiting and only supportive therapy is required. More severe syndromes are sometimes reported as exemplified by two patients who ingested the mushroom *Chlorophyllum molybdites* and developed severe gastrointestinal symptoms requiring hospitalization [7]. Mushrooms of the *Lepiota* generus may also contain varied toxins and it is likely that new toxins will be identified to explain ill-understood syndromes.

The ingestion of raw mushroom may also be associated with gastrointestinal disturbances due to the presence of toxic thermolabile substances in many mushroom species. An immune-mediated reaction is also possible with some mushroom species leading to food intolerance/allergy or following inhalation of spores [8].

Contamination of mushrooms with bacteria and fungi, as well as heavy metals and pesticides may also result in various adverse effects [9,10]. Finally, contamination of mushrooms by radiations has been a matter of concern following the Tchernobyl disaster as some species have been shown to concen-

trate radiations, and this is worth mentioning here even though these findings may result in long-term consequences [11].

Muscarine syndrome

Muscarine is a natural substance occurring in various *Inocybe* (e.g. *I. patouillardi*, *I. lacera*, *I. fastigiata*) and *Clitocybe* (e.g. *C. dealbata*, *C. rivulosa*, *C. cerusata*) species. In fact, many mushrooms contain either very low levels of muscarine or other toxins which mask the effects of muscarine (e.g. *Amanita muscaria*). Muscarine is a potent agonist of acetylcholine muscarinic receptors.

However, due to the low oral bioavailability of muscarine, this syndrome is usually minimal. Symptoms generally occur within several minutes or hours after ingestion and include pronounced sweating, salivation, nausea, vomiting, diarrhoea, abdominal pain, myosis, accommodation disturbances. In severe cases, bradycardia, hypotension, and bronchial obstruction may occur. Symptoms usually last 2–6 hours and are treated with the help of atropine and supportive measures, including rehydration and oxygen [12].

Pantherina syndrome

This syndrome is caused by the ingestion of *Amanita muscari*, *regalis*, *pantherina* and *gemmata*. These mushrooms contain muscimol which binds to GABA receptors, and its derivatives ibotenic acid and muscazol which bind to glutamic acid receptors [4].

The pantherina syndrome develops generally 30 min to 3 hours after mushroom ingestion and include disorientation, ataxia, agitation, accommodation disturbances, euphoria, anxiety, depression, hallucination, tremor, fasciculations and convulsions [13]. After the excitation phase, torpor and, in severe cases, coma will occur [14]. These symptoms disappear within 6 to 48 hours. Headaches may last for several days. Supportive measures include observation of the patient and short-acting benzodiazepines.

Coprinus syndrome

This syndrome is caused by the ingestion of *Coprinus atramentarius*, *alopecia*, *insignis*, *micaceus*, *romagnesiduns*, *erebhistes*, *quadrificus*, *variegatus* and *Clitocybe claviceps*. These mushrooms contain the cyclopropanone-glutamate adduct coprine which may exert direct effects or indirect effects after activation to 1-aminocyclopropanol. Aldehyde dehydrogenase inhibition is unlikely to be the mechanism involved as coprine is a poor inhibitor of aldehyde dehydrogenase.

Symptoms of coprinus syndrome typically are those of ethanol intolerance with flush, metallic taste of the tongue, tachycardia, headache, vertigo, vomiting, sweating, fasciculation, postural hypotension and collapse. They develop very shortly after mushroom ingestion but may last up to three days. Shock,

metabolic acidosis, cardiac dyrrhythmias, and myocardial infarction have been reported following disulfiram–ethanol association. These adverse symptoms can theoretically be observed after coprine–ethanol association, especially in patients with underlying cardiovascular disease [15]. Supportive measures are usually sufficient. Ethanol consumption should be forbidden.

Psilocybin syndrome

Psilocybin and its derivatives baeocystin and psylocin share some similar effects with lysergic acid diethylamide (LSD). These compounds are found in *Psilocybe* (e.g. *P. semilanceata*, *P. copelandia* and *P. caerulescens*), *Pholiotina* and *Panaelina* (e.g. *Panaeolus cyanescens*) species [6]. High doses need to be ingested to induce psychedelic effects.

Symptoms develop 30 minutes to 1 hour after ingestion. They include nausea and vomiting, and thence vertigo, hallucinations, muscle weakness, euphoria and disorientation. In children, severe complications can develop, namely convulsions and hyperthermia [16]. Sympathomimetic effects, such as mydriasis, tachycardia, and hypertension, may occur.

Paxillus syndrome

Paxillus involutus and possibly *Paxillus filamentosus*, *Clitocybe clavipes* and *Boletus luridus* cause this syndrome with usually mild to moderate gastrointestinal disorders, within 1–2 hours after ingestion. However, another syndrome may develop after *Paxillus involutus* ingestion [17]. This immuno-allergic syndrome is due to the formation of circulating antibodies resulting in immune-mediated hemolysis after a subsequent contact. One or two hours after the mushroom meal, digestive symptoms develop with nausea, vomiting, diarrhoea, and usually hypotension. In addition, signs and symptoms of hemolysis are noted with acute renal failure. Full recovery is generally attained with supportive measures.

MUSHROOM POISONINGS WITH A DELAYED ONSET

Phalloides syndrome

Even though poisonings by *Amanita phalloides* account for the majority of deaths, a number of mushrooms are potentially as toxic; these are from the *Amanita* species as *A. bisporigera*, *A. hygroscopica*, *A. ochreata*, *A. suballiacea*, *A. tennifolea*; *A. verna*, *A. verum*, *A. virosa*; from the *Galerina* species as *G. autumnalis*, *G. badipes*, *G. beinrothi*, *G. fasciculata*, *G. marginata*, *G. micolor*; *G. sucliceps*, *G. venenata*; or from the *Lepiota* species as *L. helveola*, *L. brunneoincarnata*, *L. citrophylla*, *L. clypeolariodes*, *L. heimii*, *L. josserandi*, *L. pseudohelveola*, *L. rubescens*, *L. subincarnata*.

Toxins

Amanita phalloides contain three types of thermostable cylic oligopeptide toxins: the amatoxins, phallotoxins and virotoxins. Toxicity of *Amanita phalloides* is essentially due to α-amatoxin, a cyclic octapeptide with a lethal dose of approximately 0.1 mg/kg [1]. α-Amatoxin produces severe hepatocellular damage by binding to nuclear RNA polymerase II of eukaryotic cells which results in cell death within 24 hours. The liver and, to a lesser extent, the kidney are the primary target of this toxin because of their high rate of protein synthesis. However, the toxicity of α-amatoxin on the proximal and convoluted renal tubules is still controversial [18]. The bioavailability of α-amatoxin has been estimated from animal experiments to be lower than 1%. Approximately 60% of the absorbed α-amatoxin is excreted into the bile and subsequently into enterohepatic circulation.

The blood–placental transfer of amatoxins is still controversial: a 21-year-old woman ingested *Amanita phalloides* during her 8th month of pregnancy [21]. While detectable levels of amatoxins were present in her blood, no amatoxins could be found in the amniotic fluid. Her child had no evidence of hepatic damage at birth. By contrast, a 25-year-old woman ingested *Amanita phalloides* at her 9 weeks of pregnancy [22]. She developed acute toxic hepatitis but recovered thanks to supportive measure. Her pregnancy was medically interrupted at 12 weeks and histology of the foetus evidenced toxic injury of the liver. Amatoxins are excreted in milk, and breast feeding should be stopped when *Amanita phalloides* ingestion is suspected [23].

α-Amatoxin can be detected by various assays [19] but despite recent efforts no correlation was established between α-amatoxin bound to liver tissue, plasma levels and the severity of symptoms. Jaeger et al. [19] in a study of 45 patients intoxicated with *Amanita phalloides* found α-amatoxin plasma concentrations between 8 and 190 ng/ml and between 21 and 162 ng/ml for β-amatoxin after 37.9 hours post-ingestion on average. Total fecal excretion ranged between 8.4 and 152 mg for α-amatoxin, and 4.2 and 6270 mg for β-amatoxin in 10 patients [4]. Overall, these data showing low amatoxin serum levels during the first 48 hours, marked elimination in the urine and the feces, and a significant entero-hepatic cycle have been largely considered relevant for the management of human poisonings [18].

High concentrations of amatoxins can be found in the liver 9 to 22 days after the ingestion [19]. Interestingly, tissue concentrations of amatoxins were consistently found to be markedly higher than liver concentrations. Therefore amatoxins appear to remain concentrated in the kidney and this may explain the high urinary elimination.

Phallotoxins (phalloidins) which are not absorbed by the gastrointestinal tract have however been suggested to account for the initial cholera-like symptoms [20]. The role of virotoxins is unknown, but it is at best very limited as virotoxins are not absorbed by the digestive tract.

Clinical signs

Following ingestion, three clinical phases have been typically described [1]:

– *the latent phase* always lasts 6 hours at least, usually longer, and sometimes up to 48 hours.

– *the gastrointestinal phase* is characterized by the sudden onset of severe gastrointestinal symptoms, including abdominal pain, vomiting and cholera-like diarrhoea. The clinical features are those of severe gastroenteritis and may mistakenly diagnosed as of microbial origin. Due to the usual severity of the gastroenteritis, early and severe metabolic complications are common, including renal failure, acidosis, hypoglycemia, with children at a higher risk. This phase usually lasts 3–4 days and sometimes up to 10 in severe poisonings.

– *liver injury* is the major event in *Amanita phalloides* poisonings. Usually asymptomatic hepatic failure develops as gastrointestinal symptoms improve. Hepatic enzyme levels increase either progressively within 36 to 48 hours post-ingestion, or abruptly, and this is suggestive of a severe and potentially lethal liver failure typically associated with renal failure due to deshydration and/or direct nephrotoxicity, which is still a matter of debate. In any case, renal failure is marked in very severe poisonings only. In severe liver failure, encephalopathy, hypoglycemia, will develop.

Prognosis

At best prognosis should be based on a knowledge of the actual ingested amount of toxins, which is unfortunately impossible. Although serum ALAT levels are good indicators for prognosis, the prothrombin time and factor V are the only reliable prognosis factors that can be suggested for judging the intensity of the liver failure. The largest study so far, by Floersheim et al. [24], suggested that the prothrombin time was indeed the most reliable prognosis factor. Christen et al. [25] investigated various parameters (namely coagulation factors, prothrombin time, and serum liver enzymes) in 5 people from the same family who were accidentally intoxicated by *Amanita phalloides*. They concluded that factor V was the most reliable.

Age is another important factor: mortality is more frequent in children under 12 years than in adults; Jaeger et al. [19] reported 3 deaths out of 9 poisoned children, as compared to 5 deaths out of 36 poisoned adults. It is unsure that the higher sensitivity of children is due to a greater intake of mushroom toxins taking into consideration the child's weight, as most lethal intoxications were caused by seemingly low amatoxin amounts.

Pregnant women were suggested to be at a higher risk as there have been several lethal intoxications [18]. No correlation can be found between blood amatoxin levels and the severity of symptoms.

Treatment

The treatment of Phalloides syndrome can rely on supportive measures only. Emphasis is however on fluid administration and the correction of hydroelectrolytic disturbances. Gastric lavage is likely to be ineffective due the delay of

several hours between ingestion and hospital admission even though amatoxins have been found in fluids of gastric lavage performed after 36 to 48 hours [19]. However, administration of activated charcoal is considered to be useful owing to the enterohepatic circulation of α-amatoxin. Forced diuresis has been suggested to enhance elimination of α-amatoxin (60–80% is eliminated within 2 hours) but it is not yet established whether α-amatoxin nephrotoxicity is enhanced by forced diuresis. In contrast, other detoxification procedures, for example hemodialysis, hemoperfusion or plasma exchange, have not been shown to be of value.

Specific treatment is limited despite continued efforts to identify potent antidotes: penicillin G and silibinin which were suggested to prevent α-amatoxin uptake by hepatocytes are usually recommended [20,26] even though their efficacy remains to be clearly established. In addition, silibinin could enhance α-amatoxin elimination by reducing the enterohepatic circulation and by stimulating DNA-dependent RNA-polymerases. Even though convincing clinical trials of silibinin in *Amanita* poisonings are still awaited, animal results have provided evidence for silibinin efficacy [27].

Older potential antidotes such as thioctic acid, or more recent candidates, such N-acetylcysteine, were not associated with conclusive results, at least in experimental animals. N-acetylcysteine administration did not protect mice whatever the endpoint, namely survival or transaminase increase [28]. However, a clinical study of 86 patients [29] treated with N-acetylcysteine (intravenous bolus of 150 mg/kg, then continuous intravenous infusion of 50 mg/kg every 4 hours) in additional to supportive measure and gastric lavage, evidenced a seemingly reduced mortality as 7% only of patients with a severe poisoning (ALAT > 2000 UI/l) died.

In fact, the best therapeutic measure nowadays is heterotopic liver transplantation [30–32]. Criteria for heterotopic live transplantation are major coagulation disorders, such as factor V below 10%, prothrombin level below 10%, peak prothrombin time > 100 seconds, and/or encephalopathy and acidosis. Other factors of lesser value include hyperbilirubinemia, (>25 mg/dl) and hypoglycemia.

According to several authors [33,34], phalloides poisonings are lethal when hepatitis is severe. When a moderate hepatic encephalopathy is noted (stage < II), they advise basing the indication for liver graft on major coagulation disorders, prior to the occurrence of symptoms of severe encephalopathy. This is confirmed by the study of Wright et al. [36] reporting four cases of phalloides poisoning with moderate encephalopathy, but major coagulation disorders (prothrombin level < 10%); the histological examination of the liver showed a major and irreversible subtotal necrosis of the liver. In contrast, Castella et al. [37] and Lopez et al. [38] suggested that major changes in coagulation are not evidence of a severe poisoning: their patients with prothrombin level below 10%, TCA above 69 seconds and TGP at 12.221 U/l did not undergo liver graft. They were treated with hemodialysis and correction of hydroelectrolytic disturbances with a full recovery of hydroelectrolytic and coagulation disorders

within 7 days with a progressive recovery of hepatic enzyme levels and renal function.

Another important aspect of *Amanita phalloides* poisoning is the occurrence of subsequent chronic hepatitis. According to several authors, chronic hepatitis would be seen in 12% of poisonings, of which 58% had a moderate to severe poisoning. The liver injury was evidenced by liver biopsy after six months post acute poisoning. Similar findings have been reported by Fantozzi et al. [39] who noted an evolution to chronic hepatic failure in 20% of their patients. Other investigators reported that 75% of their patients with a very severe phalloides poisoning developed chronic hepatitis [40]. Although these results are hardly comparable, it remains evident that a significant fraction of patients who developed hepatitis following *Amanita phalloides* ingestion are likely to develop chronic hepatitis, and that some of them may benefit from liver graft [20].

Orellanus syndrome

Several *Cortinarius*, namely *C. orellanus*, *C. speciosissimus*, *C. splendens*, contain the bipyridine derivative orellanin which has a direct toxic effect on renal epithelial cells. In addition to orellanin, three cyclic peptides, cortinarin A, B and C have been identified of which the first two are nephrotoxic in animals.

The kinetics of orellanin in humans is poorly, if at all, known. A plasma concentration of 6.12 mg/l was found in one patient 10 days after mushroom ingestion and orellanin concentrations in renal biopsies ranged between 280 mg/g and 3000 mg/g. The renal biopsy at day 13 post-ingestion found significant levels of orellanin and orellin, (with an amount of orellanin equivalent to 7 μg per 25 mm^3 of renal tissue) while the amount of orellanin was 24 μg per 8 mm^3 of renal tissue at day 180. These results show the slow and important fixation of orellanine and by-products in renal cells, with a persistence in tubulo-interstitial cells which may account for the reported evolutive interstitial fibrosis shown on electronic microscopy at day 180 post-ingestion [41,42].

The long latency of clinical signs in relation to ingestion, and the high individual sensitivity are two characteristic features of Orellanus poisonings. Symptoms typically develop 36 hours after ingestion and include non-specific digestive signs (abdominal pain, nausea, vomiting, diarrhoea) and later, general symptoms including headache, chills, thirst and oliguria. Acute renal failure usually develops 30 hours to 17 days after mushroom ingestion [43]. Hemodialysis is required in most patients either at an early stage due to acute renal failure or when end-stage renal failure is developed [44]. The renal injury may be irreversible or partly reversible over several months or even years, and therefore will require permanent hemodialysis, and possibly kidney transplantation, but renal failure recedes within one month in 2 thirds of patients.

The addition of amino acids for 10 days has been advocated [41]. Indeed, amino acids have been shown to improve the regeneration of tubular cells after toxic necrosis, as well as dilthiazem because of its vasodilating and anti-is-

chemic effects. Whether detoxification measures such as plasmapheresis or forced diuresis should be recommended was not established but is unlikely.

Gyromitra syndrome

Gyromitra esculenta and possibly a few other mushrooms may induce this syndrome [45]. The involved toxins are thermolabile, volatile and soluble in water. Poisoning may develop during cooking (via the inhalation of toxin-containing vapours). These toxins are N-formylmonomethyl hydrazones which may be hydrolyzed to monomethyl hydrazines. Hydrazine and several derivatives have been shown to induce tumours in rodents after long-term and daily exposure to very high doses [46]. The toxin gyromitrin has been classified as a natural food carcinogen. Teratogenic and embryotoxic effects have also been noted [47].

Gyromitra poisoning is not a major health problem in Western Europe in sharp contrast to Central and Eastern Europe as these mushrooms are very common there, sold as fresh mushrooms in markets, and sometimes exported, under the misleading name false morel [45]. As it is very difficult to determine the actual amount of gyromitrin and hydrazine derivatives in a given meal, eating *Gyromitra esculenta* is always risky and should be preferably avoided.

Symptoms develop after 6–8 hours, and sometimes up to 24 hours. They include vomiting, nausea, abdominal pain and hypoglycemia. Hepatocellular and renal dysfunction may be observed in severe poisonings. Seizures and neurologic deficits are typical of this type of mushroom poisonings, with features somewhat reminiscent of isoniazid poisonings. Treatment is essentially supportive. Pyridoxine has been suggested to be useful but this is not confirmed by animal experiments.

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V.S.G. Murray

31. Toxic plants (excluding fungi)

INTRODUCTION

Plants have a range of biologically active chemicals, some of which have an adverse effect on human health following exposure by ingestion or by skin or eye contact. The concentration of toxins may vary in different parts of the same plant and within the same species it may vary between different individuals, depending on factors such as the environment where the plant was grown and the season. The toxicity of products made from plants, such as food or medicines, may vary according to the method of harvesting, storage and preparation. The severity of poisoning varies according to the part of the plant and amount to which the patient is exposed, the route of exposure and the individual's susceptibility.

Since toxicity may vary between different species within a genus, it is important to identify both the genus and species of the suspect. However, accurate identification can be a major problem. The doctor treating a patient with suspected poisoning may not have a specimen of the plant, and have to rely on the patient's description of the plant and the common name attributed to it by the patient. Even if the patient does bring the plant to hospital, there may be no one with the expertise and the necessary information sources needed for an accurate identification. The doctor managing an individual case of suspected poisoning may be unable to exactly identify the plant and so have difficulty in deciding on optimum immediate treatment. This may be one reason for the relatively small number of case reports of plant poisoning in the literature.

In some instances, doubt exists about the accuracy of the identification of plants in literature reports of cases of poisoning. In addition, plant taxonomy is a dynamic science and the application of different taxonomic classifications may confuse the accurate identification of the species [1]. In consequence it may be difficult to assess the toxicity of a species. Therefore, possible inaccuracies in identification and differences in application of common names [2], must be borne in mind when describing the epidemiology of plant poisoning and comparing statistics from different sources.

Typical circumstances of exposures to toxic plants are summarised in Table 31.1. The most commonly reported exposures occur accidentally, and involve

children under the age of five eating attractive plant parts such as berries, flowers, or leaves of wild, garden or house-plants. Accidental exposure may occur as a result of misidentification of wild salads, vegetables, fruits, or plants used for traditional medicines. Other circumstances include exposure to plant material used or abused for recreational purposes. Dermal contact with plants causing adverse health effects may occur as a result of occupational exposure or leisure or hobby exposure.

EPIDEMIOLOGY OF PLANT POISONING

Studies of the epidemiology of plant poisoning, based on analysis of enquiries to poisons centres and admissions to hospital, show that suspected poisoning from exposure to plants is common, and a matter for concern, although not as common as poisoning from pharmaceuticals or other chemicals. Currently between 2 and 10% of enquiries to poisons information centres relate to plant and fungi exposures (most poisons centres statistics do not distinguish between exposure to plants and fungi). Cases of severe poisoning are infrequent.

The American Association of Poisons Control Centres recorded plant-related inquiries as the fourth most common category of calls received by the 73 participating poisons centres in the national data collection system of the Association [3]. For the calendar year 1991 a total of 112,564 plant related calls were analysed, which represented 6.1% of all inquiries. The ten most commonly implicated plants are listed in Table 31.1, and the potential toxicity of many of these plants can be considered as of low or of no toxic hazard.

Botanical name	Common name	Frequency	Percentage
Philodendron spp.	Philodendron	6407	5.6
Dieffenbachia spp.	Dumbcane	4242	3.7
Capsicum annuum	Pepper	3687	3.2
Euphorbia pulcherrima	Poinsettia	3289	2.8
Ilex spp.	Holly	2839	2.4
Phytolacca americana	Pokeweed	2349	2.0
Crassula spp.	Jade plant	2244	1.9
Spathiphyllum spp.	Peace lily	1969	1.7
Brassaia and Schefflera spp.	Umbrella tree	1878	1.6
Toxicodendron radicans	Poison ivy	1735	1.5
Total number of plant exposures to National Data Collection System		112 564	100%

After Ref. [3].

Table 31.1. *American Association of Poisons Control Centres National Data Collection System information on frequency of plant exposures by plant type, 1991*

Similar trends are reported from other industrialised countries. Approximately 6% of 80,000 emergency case enquiries received at the National Poisons Unit, London in 1988 involved suspected poisonings due to plants or fungi [4]. Of these approximately 50% concerned accidental poisoning in children under the age of 5; the majority of the remaining cases resulted from plant or fungus misidentification, physical contact leading to contact dermatitis, recreational use for hallucinogenic purposes or, more rarely, attempted suicide. A recent report from the Swiss Toxicologic Information Centre shows that exposure to plants rarely leads to severe toxicity [5]. A retrospective review of plant exposures as reported to Hennepin Regional Poison Centre in 1985 showed that they accounted for 3228 (10%) of all inquiries [6].

Seasonal variations in the type and frequency of enquiries to poisons centres about suspected plant poisoning are widely recognised. For instance, the New Hampshire Poisons Centre reviewed 3381 records from two three-month periods (July to September 1981 and January to March 1982) and found that significantly more plant inquiries were received in summer (306, 18.1%) in comparison with 162 (9.6%) calls received during the winter period [7].

National or regional variations in the epidemiology of plant poisoning reflect differences in the use of plants by the local community for food, traditional medicines and home-made remedies, and other purposes. Several developing countries have undertaken hospital-based surveys. In Sri Lanka, a retrospective review of 4556 cases of poisoning admitted to 27 hospitals in 1986, found only 112 (2.5%) poisoning cases where symptoms were due to exposure to plants and fungi [8]. Only 39% of the patients were aged under 15 years. Over half the patients had ingested plants known to be seriously toxic, 49 (44%) patients ingested *Gloriosa superba,* probably in suicide attempts, resulting in 8 deaths. In Zimbabwe, only 3% of 2873 children under 15 years admitted to urban hospitals between 1980 and 1989 with a diagnosis of poisoning were exposed to plants [9]. However, 699 (23%) admissions, with 619 in the under 5 age group, were the result of use of local traditional medicine, Mutti. Kasilo and Nhachi [9] considered that delayed admission to hospital resulted in the poor outcome experienced by many of these children: of those treated by Mutti 81 children died. Information on plant use in Mutti has been extensively reviewed and many of the preparations used are plant based [10]. The Poisons Control Centre in Uruguay reported a significant number of cases of plant poisoning in women who used home-made preparations of plants as abortifacients [11]. The International Programme on Chemical Safety (WHO/ILO/UNEP) has recently undertaken a survey of 69 poisons information centres working in all World Health Organisation Regions in order to obtain a worldwide perspective on the number, type, and severity of plant exposures [12]. Only provisional data has been made reviewed so far but it is intended that detailed analyses will be made available within the next year.

TOXIC PLANT POISONING

In order to provide pragmatic data on plant poisoning, the information is presented by circumstances of exposure. Thus this section is concerned accidental ingestion in childhood, and accidental ingestion by erroneous identification of edible plants and naturally occurring toxicants, intentional exposure for suicidal and recreational purposes, accidental and occupational exposure to dermatitis causing plants and traditional medicines: inaccurate identification, iatrogenic exposure and adverse drug reactions.

Accidental ingestion in childhood

Litovitz and Manoguerra [13] reviewed 3,810,405 exposures involving children younger than 6 years of age reported to poisons centres in the United States between 1985 and 1989. Plant exposures were one of the three most commonly implicated substance categories with 375,649 (9.8%) inquiries, 33 of these were cases where children were reported to have experienced major clinical effects. Only one fatal paediatric plant poisoning was found following exposure to *Conium maculatum* (Hemlock). Although toxic plants present a hazard, this data demonstrates a relatively low toxic risk from accidental childhood exposure to plants.

In many instances these childhood incidents involve the ingestion of low toxicity or non-toxic plants, for example *Solanum pseudocapsicum* (Christmas cherry). Recently, the National Poisons Information Service (NPIS), London, reviewed the plants associated with childhood incidents and have identified several further species which, on acute exposure, present low or non-toxic risks; these include:

Begonia spp.	Begonia
Chlorophytum spp.	Spider plants
Cotoneaster spp.	Cotoneaster
Fuchsia spp.	Fuschia
Lonicera spp.	Honeysuckle
Mahonia spp.	Mahonia, Oregon Grape
Quercus spp.	Oak — pedunculate, sessile and holm)
Pyracantha spp.	Pyracantha, Firethorn
Saintpaulia spp.	African Violet
Tradescantia spp.	Tradescantia
Yucca spp.	Yucca

As a result of this review, a poster, "*A guide to commonly ingested non-toxic substances for Accident and Emergency Departments*" has been published which lists these plant species along with other substances and products which on acute exposure present low or non-toxic risks [14]. The poster is targeted at medical professionals and is in part intended to reduce the number of inquiries coming to the Service.

However, the potential hazard from exposure to toxic plants may be so serious that in some instances serious accidental childhood poisoning may occur. The following summaries, containing recently reported data, highlight plants known to have given rise to serious paediatric poisoning worldwide.

Dieffenbachia (Leopard lily, Dumbcane). A member of the Araceae family, *Dieffenbachia* is widely used as a house-plant in many cultures, and has resulted in many inquiries to poisons centres as a result of accidental childhood exposures. All parts of *Dieffenbachia* contain irritant toxins including calcium oxalate needles (raphides) and oxalic acid and possibly saponins, glycosides, alkaloids, proteolytic enzymes, protein-like substances and cyanogenic glycosides. Their presence and involvement in toxicity is the subject of much confusion since the mechanisms are still not fully understood, despite much study. The calcium oxalate needles (raphides) are present in ejector cells and pressure causes these cells to open and the contents to be released. The needles may penetrate mast cells leading to histamine release. It may be that oxalic acid is also present in the ejector cells and is transferred with and ejected by the needles [15]. There is the suggestion that penetration by the proteolytic enzymes enhances the damage caused by the calcium oxalate crystals [16].

Following ingestion the following clinical effects have been recorded including a burning sensation in the mouth, vomiting, severe diarrhoea, salivation, difficulty in swallowing and, sometimes, loss of speech and impairment of airway patency [15]. Physical effects may be complicated by systemic toxic effects causing bradycardia, muscle twitching and cramps and respiratory failure [17]. Deaths from ingestion of *Dieffenbachia* have been reported [18]. Death of an 11-month-old child was attributed to effects secondary to erosions caused by ingestion of the leaves of *Philodendron*, another member of the Araceae family [19]. In a recent retrospective review by the Pittsburgh Poisons Centre [20], 188 cases of ingestion or suspected ingestion of *Philodendron* or *Dieffenbachia* were identified with 72% of these cases concerning children aged 4–12 months. In all these cases the integrity of the leaves was reported as being broken. Surprisingly, only three cases concerning exposure to *Dieffenbachia* and one to *Philodendron* were considered to have resulted in clinical effects: in these four cases symptoms occurred within five minutes and were of short duration with no serious oral complications or delayed symptoms being noted. This data suggested that even plants thought to present a real toxicological hazard are in fact of low risk. However, the IPCS survey shows that *Dieffenbachia* caused the most number of symptomatic cases worldwide [12]. Therefore, the clinical effects of the Aracaea family, although relatively rarely documented in the literature, can be so severe that the whole family should be regarded as hazardous.

Kalmia latifolia (American laurel, Mountain laurel, Calico bush). Children have been poisoned in the USA after sucking nectar from the flowers [21] and the reported clinical effects include a burning sensation in the mouth, salivation, rhinitis, vomiting, diarrhoea, bradycardia and, in severe cases, coma and death. However, toxicity is variable and one study concluded that plants

cultivated in central Europe contained little or none of the toxin responsible, acetylandromedol (also known as andromedotoxin and grayanotoxin I) [22].

Laburnum anagyroides (Laburnum, Golden rain, Golden chain) Although all parts of *Laburnum anagyroides* are toxic, especially the bark and seeds, most childhood ingestions, often by 5–12 year olds who are attracted to the seeds and pods, result in few serious clinical effects [23]. Ingestion of whole pods or seeds alone is likely to cause vomiting and possibly drowsiness, headache and tachycardia [24].

Lantana camara. The unripe fruits are toxic and are considered to be attractive to children. However, only two published reports are available. Morton [18] reported four cases of poisoning occurring in 1961–2, in Tampa, Florida, in children who had ingested berries of *Lantana camara*: one died of neurocirculatory collapse after chewing and swallowing the unripe, green berries; another child, swallowed but did not chew the berries and survived, and two other children suffered acute poisoning. Seventeen cases of poisoning were described in children, all aged under 6 years, over a 2-year period. The children had eaten an undetermined number of fruits, but three of them had clinical effects and one, who unlike the others, did not vomit, collapsed and died [15].

Nerium oleander (Oleander). The whole plant is extremely poisonous, especially the seeds, and contains cardiac glycosides of the cardenolide type [15], especially oleandroside and nerioside [26]. These toxins have a digitalis-like action. One leaf is reported to be potentially lethal to humans [26]. The toxicity of the plant is unaffected by drying or boiling [27]. Children find the flowers attractive and have been poisoned by sucking out the nectar. The first clinical effects of poisoning occur within a few hours: numbness of the tongue, abdominal pain, nausea, vomiting and diarrhoea (sometimes with blood) and tachycardia. Dilation of the pupils and visual disturbances have been reported. More serious cases are identified by the presence a slow, weak, irregular pulse and hypotension, possibly resulting in death [27].

Ricinus communis (castor-oil plant). Ingestion of attractive seeds such as those of *Ricinus communis* (Castor oil), a native of the tropics, sometimes used to make decorative necklaces, can pose a serious risk of accidental childhood poisoning. Recent concern that this might occur in the U.K. following the sale of necklaces by a charitable organisation resulted in the recall of 1151 imported necklaces made from *Ricinus communis* which were put on sale in 346 shops between 8 and 17 June 1993 [28]. Fortunately, only one suspected case was identified from this source by Toxicovigilance carried out by the National Poisons Unit (NPU), London and did not result in serious ill health of the child involved [29].

All parts of the plant are toxic; the seeds, which are attractive in appearance, contain the highest concentration of ricin and low-molecular weight glycoproteins with allergenic activity [15]. The release of ricin depends on the content within each seed and how thoroughly the seeds are chewed [27]. The clinical effects of poisoning usually appear after a latent period of two to 24 hours or

more and include violent vomiting, abdominal pain, profuse watery or bloody diarrhoea (sometimes lasting several days and causing severe dehydration), dilation of the pupils, shivering and fever. Marked volume depletion, electrolyte disturbances, hypotension and tachycardia with circulatory collapse have been reported [15]. Radioimmunoassay of biological samples from the patient can assist in confirming the diagnosis of ricin poisoning if the history of exposure is not readily obtainable, but the assay is not widely available and is of variable reliability. Clinical management relies on early gastrointestinal decontamination with emesis and repeat-dose activated charcoal. Supportive care with fluid replacement and the possible use of urine alkalinisation which may prevent acute tubular necrosis are the treatment of choice, as no specific antidote to ricin is known. In sensitised patients, ingestion may cause immediate respiratory difficulty, facial oedema and lacrimation leading to death within 30 minutes. One allergic reaction resulted simply from biting into a bean [30]; a similar reaction in a 22-year-old female was recently reported to NPU [31].

Accidental exposure by erroneous identification of poisonous plants

Although this topic is also discussed in Chapter 32, the problems of inaccurate identification are sufficiently important to merit some comment here. The following eight plant summaries provide some recent data on those plants, bulbs and tubers commonly confused with edible plants, bulbs and tubers.

Poisonous plants mistaken for edible species

(1) *Atropa belladonna*. The glossy black berry of *Atropa belladonna* (Deadly nightshade) has been implicated in acute poisoning or suspected poisoning when mistaken for edible wild berries (e.g. *Vaccinium myrtillus*, Bilberry) [27]. The berries contain a variable mixture of tropane alkaloids, the proportions and quantity varying according to season and growing conditions: unripe berries containing mostly L-hyoscyamine and ripe berries mostly atropine.

Ingestion of one ripe berry can produce obvious adverse anticholinergic effects including dilated pupils, tachycardia and a hot, dry skin with delirium. Symptoms are usually rapid in onset and may persist for several hours. One family ate approximately 150 g each of stewed berries resulting in gastro-intestinal symptoms, convulsions and, in one case, coma. All recovered within six days after supportive medical care [27]. Serious cases are relatively infrequent but the benefit of rapid identification of *Atropa belladonna* L. (Deadly nightshade) is of considerable benefit because it is frequently confused with other nightshades (*Solanum* spp.), to which it is distantly related.

(2) *Cicuta douglassi* (Douglas Water hemlock). A recent fatal case of accidental misidentification of *Cicuta douglassi* for watercress is documented by Litovitz et al. [31]. A 32-year-old female was picking watercress along a stream bank and ingested a root. Within 30 minutes of ingestion, she developed status epilepticus which did not respond to diazepam or phenytoin given one hour

later. The patient was paralysed and ventilated but seizure activity could not be controlled during eight hours and she died four days after exposure. Plants submitted were identified as *Cicuta douglassi* (water hemlock) and *Conium maculatum* (Hemlock), both poisonous, and *Rorippa* spp. (Yellow Cress), which is considered to be of low or no toxicity.

Hemlock water dropwort poisoning has resulted in well described neurotoxic effects, but Rizzi et al. [32] also describe associated rhabdomyolysis and acute tubular necrosis in 18 cases of accidental hemlock poisoning occurring between 1971 and 1990.

(3) *Digitalis purpurea* (Foxglove). Serious cases of accidental poisoning from *Digitalis purpurea* (Foxglove) are rare, but it has been mistaken for spinach and other leaf vegetables. Simpkiss and Holt [33] reported a case concerning a mentally retarded boy who ingested green parts of the plant; his plasma digitoxin concentration was 122 μg/l (therapeutic concentrations are usually below 25 μg/l). His clinical signs included vomiting, bradycardia and complete heart block, along with increased plasma electrolytes, but he recovered after 18 days.

On ingestion, spontaneous vomiting (sometimes persisting for more than 24 hours), frequently occurs reducing the absorption of the cardiac glycosides, such as digitoxin and digitalin [27] and saponins [34] such as digitonin, gitonin and tigonin [35]. Other clinical effects of poisoning include nausea, abdominal pain, diarrhoea, headache and bradycardia. In severe cases xanthopsia (disturbance of yellow vision), trembling, convulsions, delirium and hallucinations may develop [27].

(4) *Hyoscyamus niger* (Henbane). All parts of *Hyoscyamus niger*, particularly the seeds, contain a mixture of the tropane alkaloids hyoscyamine, hyoscine (scopolamine) and atropine [34]. The clinical effects documented include dry mouth, diplopia, mydriasis, nausea, mental confusion, excitability, muscular weakness, tachycardia and hallucinations. In serious but rare cases, coma and death from heart failure and respiratory failure have been reported [27,34].

A report of a group of Turkish children who ate Henbane leaves rather than an unspecified salad leaf resulted in a childhood fatality [15]. The roots have also been eaten in mistake for those of *Chichorium intybus* (chicory), *Pastinaca sativa* (wild parsnip) and *Armoracia rusticana* (horse radish), with occasional fatal consequences [36].

Poisonous bulbs and tubers mistaken for edible species.

(1) *The bulbs of Hyacinthus orientalis* contain the highest concentration of toxins, of which lycorine is thought to be present and occasional poisoning cases have arisen from the bulbs being eaten in mistake for onions. Lycorine acts as an emetic [35]. Clinical effects have included nausea, vomiting, diarrhoea and stomach cramps, with excessive salivation [27].

(2) *Narcissus* (Daffodil, Jonquil) bulbs have often been mistakenly eaten for onions since they too are often stored, like onions, in kitchens. These bulbs

contain at least 15 alkaloids and oxalic acid which are not destroyed by cooking. Ingestion of less than one bulb in adults or children has produced marked nausea, vomiting, abdominal pain and diarrhoea [37].

(3) *Tulipa* bulbs are known to contain lectins, which are gastrointestinal irritants, as well as the lactones tulipalin A and B and a glycoprotein [35]. Clinical effects of poisoning are nausea, vomiting and increased salivation. A number of cases refer to the use of tulip bulbs in mistake for onions. In 1978, five people ate a goulash cooked with tulip bulbs; within 10 minutes they developed sweating, vomiting, intense salivation and breathing difficulties. One patient developed palpitations but all recovered with symptomatic treatment. In another case, five bulbs have been reported to have produced slight gastro-intestinal symptoms [15].

(4) *Gloriosa superba* (Glory lily). The tubers are particularly poisonous [26] and several recent case reports are available where adults have been poisoned by ingesting these tubers in mistake for *Ipomoea batatas* (sweet potatoes) or other root vegetables. In one report, an adult, who ate 125 g of tubers as part of a meal, survived after receiving vasopressors, fluid replacement and steroids, but developed hair loss [35]. In another case, a 95-year-old male died after mistaking *Gloriosa superba* for an onion and adding it to a stew [31]. Following ingestion, he developed severe diarrhoea, vomiting, weakness, tachycardia and hypotension of 95 mmHg. He was treated by gastric lavage and was given activated charcoal and fluids. He became anuric with raised creatine, AST, ALT and alkaline phosphatase, and a prolonged clotting time. He died on the third day of admission.

The tubers of *Gloriosa superba* contain the alkaloids colchicine and gloriosine, both having an antimitotic effect arresting cell division, with salicylic acid and resins. Each gram of *Glorisa superba* tuber has been found to contain approximately 3 mg of colchicine. It is considered that the estimated fatal amount of pure colchicine is 7–60 mg, therefore even a small amount of the tuber could cause serious poisoning [35]. Clinical effects reported following ingestion include cramp, vomiting, diarrhoea, numbness of lips and tongue [30], difficulty in swallowing, dehydration, tachycardia and severe hypotension. These symptoms may be followed by collapse, fits, paralysis, bone marrow depression and death which is usually due to respiratory failure.

Accidental exposure to naturally occurring toxicants

Poisonings caused by naturally occurring toxicants can be classified as plant poisonings. Acute and chronic accidental poisonings are extensively reported and problems of identification are a cause for concern.

Rheum hybridium (Rhubarb). This plant provides a fascinating example of naturally occurring toxicants within a plant that is a well recognised and safe food source. All parts of the plant, especially the leaves, contain oxalates of calcium or potassium and oxalic acid [26] and, in addition, the leaves are also thought to contain anthraquinone glycosides. There is little hazard in eating

the red leaf stalks when cooked but it is unwise to eat raw leaf stalks or any other plant part [24].

Within an hour, ingestion of the leaves or raw plant can cause a range of symptoms including severe abdominal pains, nausea, vomiting, weakness, difficult breathing, burning of the mouth and throat, drowsiness, muscular twitching and, in severe cases, convulsions, coma and death. On recovering from the initial illness, the patient is at risk of developing delayed liver and kidney damage [26]. Many cases of poisoning from eating the raw and cooked leaves were sporadically reported during the First World War in Britain when this practice was recommended because food was scarce, and some fatalities resulted [24]. Within western culture an increasing desire for natural food and "food-for-free" have led to instances of poisoning which have sometimes been severe. The following summary provides examples of acute poisoning by naturally occurring poisons.

Sambucus mexicana (Elder, Elderberry). Although the berries are well known as being harmless when cooked or processed, fruits and other plant parts contain cyanogenic glycosides. Following consumption of a juice prepared from crushed berries, leaves and stems of *Sambuccus mexicana*, 11 people developed nausea, vomiting, abdominal pain and weakness [38]. One patient became unconscious and was admitted to hospital with possible cyanide poisoning. All recovered without treatment. Mistaken identification and modern harvesting methods can result in accidental product contamination as the following summary demonstrates.

Solanum nigrum. Accidental contamination by unripe green *Solanum nigrum* (Black nightshade) of 2 lb packets of commercially available frozen sliced green beans sold in the UK and imported from Belgium resulted in several cases of solanine poisoning [39]. Nausea, abdominal pain, vomiting and diarrhoea occurred seven to ten hours post exposure, but only two children required 24-hour observation in hospital. Chronic poisoning from naturally occurring toxicants can result from direct or indirect contamination of food products.

Kalmia latifolia (American laurel, Mountain laurel, Calico bush). Honey contaminated by the toxins found in the nectar of *Kalmia latifolia* has been identified, but no fatal consequences were discovered [34], however toxicity is variable and one study concluded that plants cultivated in central Europe had little or no content of active substances [22].

Lathyrus odoratus (Sweet pea) and the *Leguminosae* family. Haimanot et al. [40] judge that lathyrism has been known since the time of Hippocrates (460–377 BC). Reviews of the neurotoxic effects of lathyrism identify epidemics which have occurred in North Africa, the Middle East, Asia and the Indian subcontinent. Recently reports of neurolathyrism suggest that it has become endemic in Ethiopia, India and Bangladesh [40]. The seeds of *Lathyrus odoratus* resemble edible peas. All parts of the plant are toxic, particularly the seeds, however poisoning from this genus is only a hazard after four to eight weeks of chronic ingestion of the plant material. Symptoms include paralysis, brady-

cardia, shallow breathing, muscular tremors and convulsions, and severe cases are potentially fatal [26].

Intentional exposure for suicidal purposes

Plant exposure for suicidal purposes is fortunately rare. Most cases suggest that patients ingest more than one toxic substance if intending to commit suicide [3,31], but experience from elsewhere in the world suggests that only one plant substance is taken.

Aconitum napellus (Common monkshood). All plant parts are highly toxic. It is considered that the lethal dose of aconitine for an adult is 3–6 mg; only a few grams of plant material can cause severe or fatal cardiac poisoning [27]. The alkaloid content of a single plant varies considerably with soil type and season; in winter and spring the roots are particularly poisonous [15,27]. Symptoms of poisoning occur rapidly after ingestion, sometimes within 10–20 minutes [15]. A characteristic tingling spreads over the body, accompanied by voluntary muscle twitching and a weak and irregular pulse [41], followed by sweating, vomiting, diarrhoea, paralysis and intense pain. Death results from respiratory paralysis or cardiac arrest. A recent fatality from the ingestion of *Aconitum* root by an adult male botanist was recorded in 1992 [42].

Digitalis purpurea L. (Foxglove). All parts of the plant are toxic, containing cardiac glycosides such as digitoxin and digitalin, and it is thought that the ingestion of two to three dried leaves could represent a fatal dose [15]. Symptoms of poisoning include nausea, vomiting (sometimes persistent for more than 24 hours), abdominal pain, diarrhoea, headache and bradycardia. In severe cases, trembling, convulsions, delirium and hallucinations have been reported. Early management, preferably within four hours, with gastric lavage leaving activated charcoal in the stomach is recommended. Urgent biological analyses should be carried out. Raised digoxin levels and/or arrhythmias, heart block or a high or rising potassium should be managed by the use of digoxin-specific Fab antibodies (fragments of sheep anti-digoxin immunoglobulin molecules bind with high affinity digoxin and other cardiac glycosides, so removing the poison from receptor sites in the tissues (see Chapter 11).

A 32-year-old man who ingested a decoction of *Digitalis purpurea* (Foxglove) and *Laburnum* in a suicide attempt, experienced vomiting, episodes of heart block, bradycardia and raised potassium levels (symptoms mostly resulting from the foxglove component of his decoction); he recovered [43].

Taxus baccata (Taxus, European Yew and other *Taxus* species). *Taxus baccata* is found in many temperate countries. All parts, with the exception of the fleshy red arils (fruit-flesh), contain the alkaloids taxine A and B, ephedrine, taxiphyllin, a cardiac glycoside and five to eight other unidentified compounds [44]. Symptoms reported following ingestion include vomiting, diarrhoea, dilated pupils, dizziness, lethargy, bradycardia, hypotension, dyspnoea, convulsions and coma [44]. Death is usually due to respiratory or heart failure. Clinical management relies on early gastro-intestinal decontamination

and supportive care as there is no known antidote to taxines.

Intentional ingestion leading to death is rare but documented case reports of fatalities include adults eating leaves [45–47] and deliberate ingestion of decoctions of leaves and bark [48,49]. An adult male died after a presumed intentional ingestion of leaves of an unspecified *Taxus* [50]. A recent fatality from the ingestion of a herbal milkshake containing *Taxus baccata* by an adult male was documented in 1991 [51], but was given an open verdict by the Coroner assessing the patient's intent.

Thevetia peruviana (Yellow oleander). The action of the cardiac glycosides present in *Thevetia peruviana* is demonstrated by the following three case reports. Misra [52] described a case of a south Indian housewife who consumed a few seeds of *Thevetia nerifolia* for suicidal purposes. She developed burning and dryness of the throat, vomiting, diarrhoea, bradycardia, tetanic convulsions and died. He considered that such cases are rare even though he had seen two such cases of poisoning in six months whilst working in a major northern Indian hospital.

A recent report of thirteen suicidal ingestions of *Thevetia* (yellow oleander) seeds showed that ingestion of four or more seeds resulted in a poor outcome particularly if the patients presented later than four hours after intake [53]. Saravanapavananthan and Ganeshamoorthy [54] reviewed 170 cases of poisoning, occurring between 1983 and 1985, arising from the ingestion of fruits and kernels of *Thevetia peruviana* (yellow oleander), a very common plant in northern Sri Lanka. Of the 170 patients, 67% were females, with 65% aged between 16 and 25 years. The commonest presenting symptoms included vomiting (68%), dizziness (36%) and diarrhoea (22%), with patients more severely poisoned developing a range of ECG changes including atrio-ventricular block (52%) and bradycardia (50%). Only seven cases died. Clinical management relies on early gastro-intestinal decontamination and supportive care monitoring and correcting of cardiac and electrolyte disturbances. Digoxin specific Fab antibodies may confirm ingestion but, as yet, have an uncertain place in the therapeutic management.

Intentional exposure for recreational use

A wide variety of plants have been used for recreational purposes (see Chapter 17). In China, the herbal use of *Cannabis sativa* (Marijuana) dates back to 2737 BC, and is currently thought to be the second or third most commonly abused substance in western culture. *Papaver somniferum* (opium poppy) is grown for the extraction of the dried latex (opium) which contains some 25 alkaloids including morphine, and for the manufacture of its derivatives. Addiction to opium or its derivatives morphine, heroin or codeine is not uncommon and illegal trafficking promotes their availability [26]. However, problems of adequate identification of the plants remain important and two examples of less commonly abused plants are given below.

Brugmansia Pers. Tree Daturas (including Angel's Trumpets). *Brugman-*

sia is the currently accepted scientific name for all shrubby species of plants previously called *Datura*. Because of this relatively recent reclassification, the nomenclature of the *Brugmansia* group has become confused in the horticultural and toxicological literature and as a result it is often impossible to determine the correct identity of species described with any certainty [55]. Although toxicity varies slightly between different species of the *Brugmansia* [56], all should be regarded as potentially psychotropic since they contain tropane alkaloids, mainly hyoscine (scopolamine) and hyoscyamine [35] which affect the central nervous system [15]. This genus appears to be well-known amongst adults and teenagers for its hallucinogenic properties.

Following ingestion, visual hallucinations alternating with violent excitement, with hypertension, tachycardia, pyrexia, mydriasis, hyperactive deep tendon reflexes, confusion, coma and sometimes death, occurring as a result of respiratory paralysis have been reported [57]. In one case, symptoms occurred 5–10 minutes after drinking tea made from the flowers; in another, within an hour after seed ingestion, and another between 1 and 3 hours after leaf ingestion [35]. In 1989, a 76-year-old man ingested 3 teaspoons (15 ml) of a home-made wine made from *B. suaveolens*. A sample of the wine proved to contain 29 mg of hyoscine/ml, resulting in a total dose of 435 mg. One and a half hours after ingestion the man developed muscle weakness, partial paralysis and dyspnoea [57].

Datura stramonium (Datura, Thorn-apple, Jimson weed). All parts of the plant contain toxins including tropane alkaloids hyoscyamine and hyoscine (scopolamine) which block the parasympathetic nervous system, atropine and nitrates may also be present [27]. Heating or drying does not reduce their toxicity. The highest levels are found in the flowers and seeds but concentration may vary greatly according to local environmental conditions and degree of maturity. Ingestion of *Datura stramonium* (Jimson weed) a plant common in rural areas of the United States, for hallucinogenic purposes, remains a problem and can result in toxicity commonly seen in cases of atropine poisoning [58].

Following ingestion, clinical effects may appear within 1-2 hours and include dryness of the mouth, skin flushing, mydriasis, nausea, drowsiness and pyrexia, tachycardia, irregular heart beat, hallucinations and, possibly, abnormal behaviour. In serious cases, delirium, convulsions, coma and sometimes death may follow [27]. Any visual impairment may last a couple of weeks. A man was poisoned after drinking a herbal tea made from *Datura stramonium* (jimson weed) leaves; it was estimated that 10–15 mg of alkaloids were ingested resulting in blurred vision, hallucinations and thirst, together with unusual and uncoordinated behaviour [27]. The leaves of *Datura meteloides* were recently implicated in a cluster of cases where the plant was consumed for hallucinogenic purposes; one of the teenagers involved experienced hallucinations for over 48 hours after ingestion of the leaves and continued to have recurrences 3 weeks later.

Accidental and occupational exposure to dermatitis-causing plants

Single acute accidental exposure of adults, for instance those who garden for pleasure, and of children at play have resulted in cases of significant plant dermatitis. Occupational exposure in gardeners, florists, the horticultural trade, herbalists, botanists, food handlers and foresters have also shown that many plants can be associated with cutaneous reactions following more chronic, repeated exposures [59]. A recent publication by Lovell [60] describes and categorises many of these cutaneous reactions to plants and plant products.

Contact urticaria

(1) *Urticaria due to injection of plant toxins.* Many plants worldwide have sharp hairs with irritant chemicals as a defensive mechanism against browsing animals. These plants are found particularly in the Urticaceae, Euphorbiaceae, Loasaceae and Hydrophyllaceae families.

The familiar plant, *Urtica dioica* (stinging nettle) has sharp hairs on its leaves and stem which deliver a cocktail of irritant chemicals on contact. Most clinical exposures lead to short term pruritis, erythema and oedema, which may on occasions persist for several days [60]. This plant, originally native to Europe, has been naturalised in temperate areas worldwide.

(2) *Immunological contact urticaria.* Many plants or plant products have been identified as causing immediate Type 1 hypersensitivity reactions in an individual following previous sensitisation [61]. On contact plant molecules penetrate the epidermis (or following inhalation or ingestion) and react with specific IgE (immunoglobulin E) bound to mast cells, leading to a release of vasoactive mediators including histamine.

Food handlers are particularly at risk from their wet working conditions and resultant maceration of the skin and have been found to be sensitive to a wide range of plants such as vegetables, fruits, nuts, herbs, spices, nuts and coffee [60,62]. Plant products in cosmetic ingredients [63] have resulted in similar hazards for hairdressers and beauticians. Essential oils known to cause contact urticaria include Balsam of Peru, eugynol, camomile, marigold and sesame.

Irritant contact dermatitis. Widely documented, irritant contact dermatitis is a response to a chemical or a mechanical insult and is not immunologically mediated [60]. Although many case reports demonstrate prolonged extensive exposure resulting in skin dryness which is frequently followed by fissuring and pruritis, some occur after single trivial exposures to the mechanical irritants of plants such as *Opuntia ficus indica* (prickly pear).

Chemically mediated irritant contact dermatitis has been demonstrated following exposure to irritant crystals such as oxalates.

(1) *Dieffenbachia* Schott. Dermal exposure to the juices or cut stems of *Dieffenbachia* Schott (leopard lily, dumbcane) a common house-plant, produces chemically mediated contact urticaria following exposure to oxalate crystals

[60]. An adult who briefly touched her mouth with a plant cutting suffered oedema, inflammation and superficial ulceration of the upper and lower lips and tip of the tongue; healing began after 3 days [64].

(2) *Hyacinthus orientalis L. sap* can produce contact dermatitis [27] but the bulbs, which have the highest concentration of oxalate crystals, have caused irritant contact dermatitis in bulb planters and sorters [60]. Irritant contact dermatitis from *Narcissus* (daffodils, jonquils) called "daffodil itch" [65] are widely recognised amongst those who handle the bulbs and who cut, bunch, pack and sell the flowers.

Phytophotodermatitis. Many plants and some plant products which contain furocoumarins cause phytophotodermatitis, in particular, members of the Umbelliferae, Moraceae and Rutaceae families.

(1) *Ruta graveolens* (rue, common rue, garden rue). Phytophotodermatitis from contact with any part of the plant coupled with exposure to bright sunlight has been frequently reported [36]. Furocoumarins, one of several chemicals found in *Ruta*, adducts with DNA in the skin, thereby giving rise to a phototoxic reaction in the presence of ultra violet A light [60].

Approximately 20 to 40 hours after contact, clinical effects recorded include painful red weal-like streaks on the sun exposed areas of the body, followed by blisters. These usually resolve to leave areas of dark brown, hyperpigmentation which may last for several months or even years [60]. Contact in sun exposed areas to *Ruta graveolens* has resulted in cases of children requiring prolonged admission to hospital for the management of up to 60% first degree body burns and even secondary contact can lead to extensive blistering on exposed parts [66,67]. However, such serious clinical reactions are uncommon.

Allergic contact dermatitis

(1) *Alstroemeria* (Peruvian lily) cultivars are grown extensively for the cut flower market in Holland, South America, USA and Australia. These plants are now one the most common causes of allergic dermatitis in wholesale and retail florists [68]. All parts of Alstroemeria contain toxins, with the greatest concentration of glycosides in the flowers. The glycosides, including 6-tuliposide, are weakly allergenic but are rapidly hydrolysed to tulipalin A, which causes sensitization [69]. It appears that the methylene group in the alpha position of the tulipalin structure is necessary for allergenic activity [35].

A recent case report describes a 54-year-old gardener who cut some *Alstroemeria* stems, was exposed to the sap through a hole in her glove and 48 hours later developed itching and dermatitis-type lesions in her right thumb, index finger and forearm. Within a few days, dermatitis developed with scaling and treatment with steroids cleared her symptoms. However, 2 months later, spotty depigmentation appeared on the hand and arm where the dermatitis had been [35]. Considerable variation in the severity of reactions has been noted; commonly, those affected are also susceptible to tulip allergens and cross-reactions may occur.

(2) *Cupressocyparis leylandii* (leyland cypress) is a popular fast-growing evergreen plant used for hedging and screening purposes in parks and gardens in Britain and elsewhere. It is a hybrid of *Chamaecyparis nootkatensis* (Nootka cypress) and *Cupressus macrocarpa* (Monterey cypress). Case reports of allergic contact dermatitis following pruning or burning have been documented [60]. Individuals previously sensitised to colophony (present in sticking plaster) appear to be particularly vulnerable; skin eruptions can be quite severe [70,71].

(3) *Primula obconica* (poison primula, German primula) is a very popular and long-established house-plant grown for its attractive flowers. Following occupational and leisure or hobby activities, many case reports of severe contact dermatitis have been documented [72–74]. In particular, the removal by hand of dead flower-heads may result in contact between the skin and the plant's resinous secretion, containing the allergen(s) [15]. This secretion can easily be carried on the fingers to other parts of the body thereby enlarging the area of exposure.

All parts of the plant are allergenic, but the allergen(s) is found principally in and on the surface of microscopic glandular hairs whose highest concentration is found on the calyx and bracts surrounding the flower head [60]. Much of the literature describes primin, a benzoquinone derivative, as the sole contact allergen responsible for dermatitis reactions. Lovell [60], however, suggests that one or more other allergens may also be present.

The primary symptom is dermatitis most often occurring on the face and hands, however, like all allergic reactions, the severity varies from individual to individual [72]. Clinical effects range from itching and burning sensations in the fingers, which may become swollen and slightly inflamed, to intense inflammation, swelling and painful eruptions in severe cases. Secondary symptoms may develop in acute cases and these include anorexia, nervous irritation and insomnia [35]. In sensitised individuals, some reports indicate that symptoms may develop after entering a room containing the plant but without any direct contact with the plant [60].

Chronic cases, due to multiple exposures over short intervals, may cause thickening and folding of the facial skin which becomes yellow-red in colour and covered with thin but tight scales, especially around the eyes [35].

(4) *Toxicodendron radicans* (poison ivy). One of the plants most widely reported to cause allergic contact dermatitis, affecting many North Americans [75] is *Toxicodendron radicans*. The potent allergen urushiol, a mixture of pentadecylcatechols is present throughout the plant [76].

Following contact an intense oedematous and vesicular dermatitis usually develops in 2 to 4 days after exposure. In particularly sensitised individuals symptoms can occur within hours and in patients not previously exposed symptoms may not develop until 3 weeks post exposure [76]. Early decontamination by washing, bathing and changing clothes within ten minutes of exposure can minimise effects [77]. Treatment with aluminium acetate compresses (1:40) and topical corticosteroids will relieve relatively mild inflammation and pruritis in 10–14 days. Occasionally systemic corticosteroids are required for severe reactions [75].

Allergenicity to *Toxicodendron radicans* can result in cross reactions to other plants, particularly the *Anacardium occidentale* (cashew nut tree). Ingestion of improperly shelled nuts led to an outbreak of perioral and more generalised dermatitis [78]. Other *Toxicodendron* species can have similar effects such as *Toxicodendron diversilobum* (poison oak) with *Semecarpus anacardium* (indian marking nut) [76].

Plant exposures resulting in more than one type of reaction

Two examples are provided of plants which cause both irritant and contact dermatitis.

(1) *Hedera helix* L. and other *Hedera* (ivy). Severe irritant and/or allergic contact dermatitis has been described after exposure to *Hedera helix* L, *Hedera canariensis* Willd. (*Hedera algeriensis* Hibb., *Hedera maderensis* C. Koch). Indeed all species of *Hedera* contain toxic, irritant and allergenic compounds in all plant parts; they are especially concentrated in young leaves and fruit. Terpenoid saponins (hederasaponins A and B, or B and C), which undergo partial hydrolysis to form α and β hederin, and rutin, caffeic acid, chlorogenic acid and emetine have been isolated from *Hedera* leaves [35]. Since these irritant and allergenic compounds are present in the leaves throughout the year, contact dermatitis can be caused during any month.

Children have developed dermatitis after climbing ivy covered walls [60]. Most adult cases of dermatitis associated with the plant arise following pruning of the plant. Such reactions can be severe and usually occur 24 to 48 hours after pruning; this is a potential hazard to professional and amateur gardeners alike. The resulting dermatitis ranges from mild to moderately severe reactions, characterized by intense itching and "nettle rash" [60]. Further, low concentrations of the irritating compounds have caused direct contact irritation during patch testing and sensitized people can develop symptoms even after handling contaminated clothing [35].

(2) *Tulipa* spp. and hybrids (Tulip). Although irritant contact dermatitis has been widely reported, allergic contact dermatitis from tulips, called tulip fingers, has been extensively documented as well [79]. The whole plant contains lactones known as tulipalins (or tuliposides) A and B, which are contact allergen [15]; and a lectin, a glycoprotein and oxalate crystals are present particularly in the bulb [60].

"Tulip fingers" is a mostly allergic contact dermatitis brought on by contact with the bulbs or their sap and is especially common in the Netherlands. In 1935, for example, a study showed that up to 85% of bulb handlers in the country had developed dermatitis [35]. Variation in harvesting techniques of the flowers affects the risk of contact sensitisation. In Sweden and Germany, for example, the bulb is split with a knife, increasing the risk of dermatitis to 60% in operatives [60]. In Denmark, the same condition accounts for some 4% of all plant-related dermatitis. Since tulip fingers is seasonal and sometimes mild it is, however, probably under-reported. Despite this, severe cases have

been reported such as the two cases described by Spoerke and Smolinske [35] resulting in serious facial swelling and speech impediment.

Occupational dermatitis and systemic absorption

Aconitum napellus L. (common monkshood). Exposure to the sap of *Aconitum napellus* can lead to characteristic prickling and tingling sensation, which may develop into vesicles. Severe occupational dermatitis in pharmaceutical workers has been reported [30]. Systemic effects following exposure has been recently documented when two women were hospitalised for 24 hours for observation after removing many lower stem leaves of cut *Aconitum* flowers over the course of a day [80].

Traditional medicines: inaccurate identification, iatrogenic exposure and adverse drug reactions

About 80% of the world's population depends on traditional medical practices [81], and the use of traditional medicines and food supplements has been increasing in many developed countries over the last few years. In contrast to conventional drugs, many people consider these products are safe and devoid of ill effects because they are natural. However, some of these preparations may cause toxic effects and only a few have been tested for efficacy, safety or quality [82]. In addition, they may not be perceived as medicines either by the consumers or their physicians. Toxicity from such products can be produced in several different ways: by the toxic nature of the substance itself [83,84], by adulteration of the product by incorporation of pharmaceuticals [85] or heavy metals [86] and by interactions between herbal medicine and orthodox drugs [82,87].

Some case reports are available where adverse health effects have occurred as a result of exposure to a traditional medicine prepared from a single plant, and two examples are given. However, most traditional remedies contain a mixture of plants, resulting in problems for toxicological interpretation; two examples are provided.

Adverse health effects from single plant traditional remedies

(1) *Eleutherococcus senticosus* (Siberian ginseng). A 70-year-old woman took one capsule daily of a food supplement containing 400 mg of root of *Eleutherococcus senticosus* (Siberian ginseng), vitamins B6 (50 mg) and E (400 IU) for 16 years [88]. She was otherwise healthy but was found to have hypertension (170/100). On stopping the food supplement her blood pressure fell to 140/80. Re-exposure to the same product on two occasions caused a rise in blood pressure which returned to normal when she stopped taking the supplement. Sonnenborn and Haensel [89] have also reported similar cases with elevated blood pressure.

(2) *Symphytum* (Comfrey). All parts of *Symphytum* species, a member of the *Boraginaceae* family (including Comfrey, Russian comfrey, Lungwort, Viper's bugloss, Borage, Forget-me-not) especially the roots and young leaves, have been found to be toxic following prolonged ingestion because the alkaloids are accumulative and overt damage may take some time to appear [90]. *Symphytum* (Comfrey) has been widely used in herbal preparations such as tablets, capsules, teas and poultices.

Many case reports exist including some fatalities from veno-occlusive disease of the liver associated with the long-term ingestion of comfrey tablets [91] and one 23-year-old man died from liver cirrhosis after consumption of steamed comfrey leaves [92]. All species of *Symphytum* contain a range of pyrrolizidine alkaloids; for instance 13 alkaloids have been identified in *S. officinale*, and 9 in *S.* × *uplandicum* [93]. The hepatotoxic metabolites of pyrrolizidine alkaloids are released by the action of liver enzymes after ingestion. The alkaloid concentration of an individual plant may vary widely depending on the age and part of the plant, and the time of the year. One study indicated that the highest concentration of the toxins occur in the roots; the lowest in leaf infusions such as herbal teas [93].

Data on the toxicity of *Symphytum* (comfrey), however, are not conclusive. Yet the British government, following the lead given by one or two other countries such as Canada, believe that there is sufficient evidence for concern and a recommendation has been issued for a voluntary ban on the sale of all tablets and capsules containing comfrey and for all products for external use containing comfrey to be labelled accordingly [94]. The use of leaves of comfrey to make herbal teas, however, is not included in this ban since the leaves are considered to have a much lower concentration of the toxins than, for example, the roots.

Adverse health effects from traditional remedies prepared from more than one plant

Poisoning by multiple plant exposure, including traditional herbal medicines, is particularly difficult to assess. The U.K. surveillance programme on toxicological problems resulting from exposure to traditional medicines and food supplements documented a case of a previously healthy woman who ingested a single dose of a herbal tea (1.8 g) recommended as a slimming aid. Within five hours she experienced sweating, abdominal cramps, diarrhoea and unwitnessed collapse [88]. She recovered completely after three hours. The tea bag contained frangula bark 35 g, senna leaf 30 g, peppermint leaf 14 g, hibiscus flowers 8 g, blacktea 5 g, goldenrod herb 5 g and lovage root 3 g. Only the first two of this list of ingredients have been recorded to cause similar symptoms to those experienced by the patient, the other ingredients have not been reported to cause adverse health effects.

From Venezuela, Guirola et al. [95] reported a recent case which proved difficult to explain toxicologically. A previously well 4-year-old boy accidentally

ingested *Jatropha gossypfolia* (tua-tua) and was subsequently treated 3 days later by his mother with a decoction of *Chenopodium ambrisoides* (pasote), piperazine, metronidazole and tinidazole. He was admitted to hospital 9 days later with weakness, protracted drowsiness and acute renal failure. He was discharged 18 days later after supportive therapy only. After reviewing the toxicological data available on all the substances, they concluded that the boy had suffered from a combination of plant poisonings.

INVESTIGATION AND MANAGEMENT OF PATIENTS

Need for identification

In cases of suspected human poisoning by plants or fungi, where appropriate medical treatment must be given without delay, rapid identification of the species concerned is vital. Physicians, however, seldom have the botanical skills necessary to make such identifications and when such expertise is unavailable the risk of inappropriate or delayed medical treatment is significantly increased. Although toxicological advice is available about plants and fungi from poisons information centres, an identification service *per se* is not usually included since identification cannot reliably be provided over the telephone. If in doubt about an identification, medical personnel can:

– *identify the plant themselves.* However, Scalise et al. [96] showed that medical professionals in Accident and Emergency Rooms had considerable problem in recognising even common plants safely.

– *resort to advice from local garden centres*, which is likely to cause some element of time delay. Rondeau et al. [97] assessed the reliability and accuracy of taxonomic identification available from plant nurseries, a source frequently relied upon for assistance by poisons information centres. Following a second identification by a trained botanist, it was found that 58% of the initial identifications by plant nursery staff were unreliable and lead to undertreatment of 24% of the study plant exposures.

– *seek advice from botanical experts* available at some Poisons Centres and at botanic gardens. This solution is far from ideal due to the time delays involved in transporting plant material and the limitation of obtaining an answer only within normal working hours.

In summary, therefore, in an emergency situation where a plant or fungus is implicated in a suspected poisoning, medical personnel face a very real problem in obtaining a fast and accurate species identification and are forced to take precautionary measures when in doubt.

After experiencing increasing concern at this situation, NPU, London, has initiated a project to develop a computerised identification system for plants and fungi, the PLATO (PLAnt TOxins) project [4]. This collaborative project between the Unit and the Royal Botanic Gardens, Kew, has been designed primarily for medical professionals, particularly those in hospital Accident and

Emergency Departments and in Poison Centres both in the UK and abroad. It is planned to make it available for their routine use by the summer or autumn of 1994. By using this system, hospitals will provide much more accurate botanical data about the plant material involved in poisonings.

Supportive and symptomatic care

With a few exceptions, some described above, there are no specific antidotal therapies available for most plant poisonings [8].

Some antidotes such as cyanide antidotes are valuable in the management of poisoning by ingestion of cyanogenic glycoside-containing plants. For example, Espinoza et al. [98] reported the effective use of sodium nitrite and sodium thiosulphate, and hydroxycobalamine, in the treatment of eight boys aged 8 to 11 years who had ingested *Manihot esculenta* (bitter casava). Other antidotes such as digoxin fragments have also been found to be useful.

Most therapeutic measures for acute exposures by ingestion include correct identification of the plant, assessment of dose response and measures to minimise absorption such as gastric decontamination. Only in severe cases is symptomatic treatment necessary and where appropriate these have been described in relation to specific plants. After acute exposure by skin or eye contact, early and thorough irrigation and decontamination are required. Usually symptomatic therapy is sufficient although some exposures necessitate systemic supportive care.

PREVENTION

In their review of 3.8 million pediatric poisoning exposure incidents, Litovitz and Manoguerra [13] consider plant exposures to present one of the persistent poisoning hazards, even though the risk of significant adverse health effects in children have been found to be very low. Nevertheless, targeting areas for vigilant poisons prevention will most effectively reduce morbidity and the associated costs. For example, a series of newspaper reports in Nigeria concerning four paediatric deaths following ingestion of *Manihot esculenta grantz* (casava) has resulted in a review of the hazards from poor processing in order to develop guidelines to make cassava safe for human consumption [99].

Many Poisons Information Centres have developed medical education material to try minimise plant poisoning. For example posters are available from the Tampa Bay Regional Poisons Control Centre, Florida, the Venom and Toxin Research Group, Singapore, and Belgium. In addition, some commercial companies have also provided poster material for education, for instance, about allergenic plants [100]. However, most of this type of information has not been evaluated to assess its effectiveness in reducing the number of incidents involving plants.

Indeed some publicity appears to increase the incidence of poisoning when a

population becomes aware of the hazard presented by certain plants. For example, Saravanapavananthan and Ganeshamoorthy [54] considered that since the publication in newspapers of the toxicity of the fruits and kernels of *Thevetia peruviana* (yellow oleander), the incidence and severity of poisoning cases had increased.

However, the need for appropriate education to the community regarding consumption of unknown or unidentified plants is likely to reduce the high incidence of plant related exposures [8]. Therefore, a new initiative in the U.K., a hazard warning labelling scheme, with monitoring for evaluation and assessment, was considered useful activity and the warnings should be placed on plants, bulbs and seeds at the point of sale by 1995 [101].

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32. Snakes

INTRODUCTION

As will be discussed later, venomous snakebites are a significant medical problem worldwide, especially in developing countries, and may affect several million people annually, with possibly more than 100,000 deaths. As statistics are incomplete at best, the true extent of this problem can only be speculated. Snake venoms do have some value, however, and are assisting in the elucidation of human physiology at the molecular level. The treatment of snakebites, especially first aid measures, remains controversial. These topics will be the subject of this chapter.

BIOLOGY AND TAXONOMY

General

Snakes are exothermic vertebrates of the Class Reptilia, Order Squamata, Suborder Serpentes. Over 3000 species are currently recognised, the majority of which are non-venomous and essentially harmless to man. Venomous species are found in five families, each discussed below. The position and anatomy of fangs is distinctive for each family. Given the scope and complexity of snake taxonomy, it is not practical to provide identifying features for each snake species or even genus within this chapter. There are a number of good regional works covering taxonomy which the reader may consult for such detailed information [1–8].

Colubrids = family Colubridae

The family Colubridae is the largest single snake family with over 2500 species, found throughout the world on all continents except Antarctica (where no snake exists). Within this family there are some species which have developed toxic salivary secretions which may enter a bite wound during the act of biting. As research into this continues, more species are added to the list of toxic colubrids. However, current evidence suggests that the majority of colubrids do

not produce toxic secretions.

A few species have developed fangs linked to a venom duct and gland, and it is these few species which are of medical significance [9]. All these snakes are opisthoglyphous, or back-fanged. This position of the fang both limits fang length and makes it less easy for the snake to effectively bite man. Nevertheless, several opisthoglyphous colubrids have very potent venoms and can cause serious envenomation and even death in man. The best known and most important of these are some South African colubrids, like the Boomslang, *Dispholidus typus* and the Bird snakes, *Thelatornis* spp. Some members of the genus *Rhabdophis*, previously thought to be harmless and widely sold as pets, are now known to have venom toxic to man, resulting in significant envenomation. A similar situation exists with some members of genus *Boiga*. In particular, the Brown Tree snake, *Boiga irregularis*, originally from Australia, has now been shown to cause significant, though non-lethal (so far) envenomation in infants on Guam, where the snake was accidentally introduced [10].

Other colubrids implicated in significant systemic envenomation include the Montpellier snake of Spain (*Malpolon monspessulanus*), the Argentine black-headed snake (*Elapomorphus bilineatus*), and the South American Culebra de cola corta (*Tachymenis peruviana*) [9]. A variety of colubrids are known to cause local envenomation without systemic problems [9]. As more species and their bites are studied, it seems probable that more colubrids will be shown to cause significant envenomation in man.

Elapids = family ELAPIDAE

Elapid snakes are typified by the cobras. All species are venomous and have well developed forward-positioned, proteroglyphous fangs. Elapids are widely distributed globally, though they do not occur in Europe. Some species, particularly in Australia, are too small to effectively bite man, but all those species able to bite man may cause at least some degree of envenomation. The fang is anteriorly placed on the maxilla, which is capable of either limited or no significant rotation. This limits the fang length, which in species dangerous to man, may range from 2 to 12 mm in length, rarely more.

Medically important elapids include: the cobras from Africa and Asia, *Naja* spp., *Ophiophagus hannah*, *Hemachatus haemachatus*; the coral snakes of the Americas, *Micrurus* spp., *Micruroides* spp.; the Mambas of Southern Africa, *Dendroaspis* spp.; the Kraits of India and East Asia, *Bungaruy* spp.; the Australian and New Guinea elapids, Brown snakes, *Pseudonaja* spp., Tiger snakes, *Notechiy* spp., Mulga and Black snakes, *Pseudechis* spp., Death Adders, *Acanthophis* spp., Taipans, *Oxyuranus* spp., Copperheads, *Austrelaps* spp., Rough scaled snake, *Tropidechis carinatus*, Small eyed snake, *Micropechis* spp.

Hydrophiids = family HYDROPHIIDAE

The hydrophiids or sea snakes are widely distributed throughout equatorial and tropical regions of the Indian and Pacific oceans, from the coast of Africa

to America. There is some evidence that they have navigated the Panama canal and are colonising the Caribbean (Warrell, personal communication). They are closely related to the Elapids, having a similar venom and fang apparatus. Medically important genera include *Enhydrina*, *Hydrophis*, *Pelamis*, and *Laticauda*.

Atractaspids = family ATRACTASPIDAE

These most unusual snakes, often called Burrowing Asps, are the subject of considerable taxonomic controversy. Their status as a separate family is not universally accepted. They are found in Africa and the Middle East. The several genera and numerous species display a heterogeneity of fang and venom gland morphology. However, the most important genus medically, *Atractaspis*, is more homogeneous, all species having anteriorly placed fangs and well-developed venom glands. The fang can be projected out of the side of the mouth and the snake can therefore bite and envenom a human without opening its mouth. Only one fang is used at a time. As will be discussed later, the venom of these snakes is quite distinctive.

Viperids = family VIPERIDAE

Viperids are amongst the best known and probably medically most important venomous snakes. They are divided into two subfamilies, Viperinae and Crotalinae. The latter encompasses all the pit vipers, so called because they have highly developed paired heat-sensing organs on the anterior part of the head in pits. These allow them to more effectively locate and strike warm blooded preys at night. All vipers have a very well-developed anteriorly placed proteroglyphous fang structure. The fangs are on a modified maxilla which is capable of considerable rotation, allowing the fang to be folded against the roof of the mouth when not in use. This has enabled development of larger fangs than in other venomous snakes of equivalent size and in some vipers fang length may exceed 2 cm. The subfamily Viperinae is found in Africa, Asia and Europe. Medically important Genera include *Vipera*, *Bitis*, *Echis*, *Cerastes*, *Causus*. The subfamily Crotalinae is found in Asia and the Americas. Medically important Genera include *Crotalus*, *Trimeresurus*, *Agkistrodon*, *Sistrurus*, *Calloselasma*, *Bothrops*, *Bothriechis*, *Bothriopsis*, *Lachesis*, *Porthidium*. There are no vipers naturally occurring in Australia or New Guinea.

VENOMS

General

Snake venoms are a complex mixture of components, with a wide range of activities. The composition is variable even within a single subspecies or a single specimen, depending on age and season. Venom is produced in paired

modified salivary glands, in most venomous snakes located superficially beneath the scales in the posterior part of the head, posterior to the eye. In some species, especially colubrids, the gland may extend well down the anterior part of the neck. The gland is linked to the fang by a duct. At least for most species, contraction of muscles around the gland compresses the gland, forcing venom along the duct to the fang. The fang may have an enclosed channel or enclosed groove or an open groove to direct the venom from the base of the fang to the tip where it exits into the bitten organism. There is some experimental evidence [11,12] and ample clinical evidence [13–16] that venomous snakes may bite a human or other organism, leaving clear fang marks, yet fail to eject any venom, or so small a quantity of venom as to be harmless. Such bites are often referred to as dry bites and it is crucial in understanding snakebite to be aware of this phenomenon. Rates of dry bites vary from species to species and may exceed 50% for some species. Dry bites occur in even the most lethal species.

In the past particular venom types have been ascribed to whole families of snakes. Thus the vipers were characterised as having hemorrhagic venoms while elapids were characterised as having paralytic venoms. Such characterisations are misleading and should not be used [17]. Some vipers cause only systemic actions including paralysis, without either local tissue destruction or hemorrhage. Some elapids cause local tissue necrosis yet no paralysis. Major clinical manifestations do vary in some very important species, depending on which part of their geographic range the snake comes from. It is therefore most appropriate to consider snake venoms in aggregate, reviewing each of the major classes of venom action/component, and later link this with venoms for each species or genera. This approach will be adopted here.

Cytotoxins

This general term can be applied to a wide variety of toxins and, as such, is rather confusing. From a clinical standpoint it is best applied to venom components causing direct or indirect cell damage at the bite site and in adjacent tissue including the capillary endothelium. In this category enzymatic components such as hyaluronidase, proteases, phospholipases are active. Possibly because the effects are diverse, these actions and components have not been studied or characterised as completely as some other actions of snake venom.

Neurotoxins

Neurotoxins are traditionally considered as those toxins directly affecting the nervous system. In general the term is usually applied to toxins affecting the peripheral nervous system, specifically acting at the skeletal muscle neuromuscular junction. More recent research has identified snake venom toxins active in the autonomic system as well [18–20].

Most widespread of the snake venom neurotoxins are the post synaptically active alpha neurotoxins (αNtx). Originally isolated from krait venom (α-bun-

garotoxin), these components are proteins which bind or are adjacent to the acetylcholine (ACh) receptor on the muscle endplate, blocking binding of ACh and so preventing neuromuscular transmission, hence paralysis. While detailed kinetics are not known, it is clear from the clinical experience that paralysis can occur within a few hours of a bite, occasionally within 60 minutes. The paralysis is often reversible using antivenom or even anticholinesterasic drugs (at least for some αNtx's). The αNtx's are found widely in Elapid and Hydrophiid venoms. In the past they were divided into short- and long-chain neurotoxins, but this distinction is now less clear. Structurally they have a three-finger appearance, with the active site near the tip of the middle finger.

Most potent of the snake venom neurotoxins are the presynaptically active beta neurotoxins" (βNtx). Again, originally isolated from krait venom (β-bungarotoxin), they are complex proteins, mostly containing a phospholipase A_2 component, often as part of a dimeric or multimeric molecule. In general they act by binding to the terminal axon at the neuromuscular junction, where they effectively cause a cessation in signal transmission by blocking ACh release. For some toxins this block is preceded by a brief facilitation of ACh release. Current research indicates that most, probably all, are ion channel toxins, affecting Na^+, K^+ or Ca^{++} channels, depending on the toxin [18,20]. While some are relatively small monomeric molecules (e.g. notexin, MW 10,000 from the Australian tiger snake), others are quite large and multimeric (e.g. textilotoxin, MW 88,000 from the Australian brown snake) [20,21]. Clinically, they often take longer to cause evidence of paralysis, but the paralysis, once established, is usually long lasting (up to 3 months) and not reversible by any known therapy, including antivenom and anticholinesterases [22]. There is often an associated damage of the terminal axon, with cellular disruption of organisation and loss of synaptic vesicles [23]. The βNtx's are found in both elapid and viperid venoms. It seems likely that they have evolved independently in several different snake lineages.

Probable autonomic effects of snake venoms, such as abdominal pain and hypotension/ hypertension have been documented. A class of snake venom neurotoxins acting on the autonomic system has been discovered in several different elapid venoms, named neuronal bungarotoxins (NBT) [19]. They were initially known as κ-bungarotoxins. They are relatively small (MW 8000), usually associate as dimers in solution, and have separate binding sites to αNtx's. Receptors for the NBTs have also been found in the frontal cortex of the CNS. The clinical importance of these toxins has yet to be established.

The mambas have several unusual classes of toxins active on the nervous system. These include the fasciculins which are potent acetylcholinesterase inhibitors; and the dendrotoxins which are specific blockers of the voltage dependent K^+ channel [18,20].

Cardiotoxins

These are closely related to the direct cytotoxins and are proteins which affect or damage cell membranes, in particular those of the myocardium,

resulting in instability and arrhythmias [24]. Cardiotoxins have been shown in some cobra venoms and more recently in Australian brown snake venom [25]. In the latter it is now suggested, based on both experimental work in animals, and clinical experience with humans envenomed, that these cardiotoxins may cause sudden collapse and death [25,26].

A second important group of cardiotoxins has been demonstrated in the venom of burrowing asps, notably *Atractaspis engaddensis*. The sarafotoxins are potent vasoconstrictor peptides related to the endothelins [27–31]. In mice they cause rapid and marked vaso-constriction of coronary vessels, severe atrio-ventricular block and a very strong positive inotropic effect not blocked by either α or β adrenergic blockers. They cause rapid death of mice due to cardiac failure secondary to cardiac anoxia induced by the intense vasospasm. The effects of these potent toxins in man are not understood or well documented, though similar effects might be anticipated.

Myotoxins

The myotoxins are closely related structurally to the βNtx's, both being based on phospholipase A_2. They cause generalised destruction of skeletal muscle either throughout the body (some elapid and viper venoms), or just locally (a few viper venoms). It is the former group, causing widespread damage, which is most clinically important. While the precise mode of action remains contentious, the sequence of muscle destruction and recovery is well documented experimentally [32–34]. In the first hour after binding to the muscle cell membrane, there is oedema confined to the extravascular space. From 1 to 3 hours there is early degeneration and hypercontraction of myofibers and accumulation of phagocytic cells. From 3 to 6 hours there is invasion of necrotic myofibers by phagocytes, collapse of the resting potential and disruption of the plasma membrane. From 6 to 24 hours there is total degeneration of individual muscle fibres, but the basal lamina and surrounding support structures remain undamaged. Muscle fiber regeneration begins at 3 days and is complete at 28 days. There is some evidence that only slow fibres regenerate.

Hemorrhagins

These venom components cause spontaneous hemorrhage, either due to damage to the vascular endothelium, or by inhibiting normal platelet function, thus blocking the first step in hemostasis [34,35]. They are usually present in association with procoagulants, fibrinogenolysins or anticoagulants, resulting in significant hemorrhage in affected patients. They are generally large metalloproteinases, and recent research has demonstrated a class of clinically significant hemorrhagins, sometimes referred to as disintegrins, which directly inhibit platelet function by inhibiting platelet-platelet adhesion through block of platelet membrane glycoprotein GP IIb–IIIa [36]. These aggregation inhibitors have been found in both viper venoms (*Calloselasma rhodostoma* and *Echis carinatus*) and elapid venoms (*Dendroaspis jamesonii*). However, structurally,

these disintegrins are quite distinctive and different from one another, the *Dendroaspis* disintegrin being structurally close to the short chain neurotoxins. All have an RGD (Arg–Gly–Asp) sequence which appears critical for activity. A hemorrhagin from *Bothrops jararaca* venom which is a zinc metalloproteinase also appears to work in a similar fashion, although it also has fibrinogenolytic and collagenolytic activity. Though not yet isolated, it appears clinically that another elapid, the New Guinea taipan, *Oxyuranus scutellatus canni*, has hemorrhagic activity in its venom [37]. This action is absent from the venoms of all other Australian elapids, at least clinically [21,22,38].

Coagulants/anticoagulants

Snake venoms contain an extensive and diverse array of components active against the hemostatic system, including procoagulants, fibrinogenolysins, anticoagulants, platelet function inhibitors and platelet aggregators [21,34–42]. Some venoms contain a number of these components, not necessarily acting in synergy. The net clinical effect in man is usually to promote bleeding, but in prey species the effects may be quite different. As an example, in birds, the powerful procoagulants may cause rapid thrombosis and death, as birds lack an effective fibrinolytic system. In man these same components usually cause a coagulopathy with defibrination and hypocoagulability and clinical bleeding. If injected IV in mammals (sheep) these same components can cause massive intravascular clotting and cardiac arrest. Thus the clinical effects of a single component depend on the hemostatic system of the victim, the quantity of venom injected and the route of entry and kinetics of distribution. This must be born in mind when assessing the effects of these complex toxins. In addition, they may activate parts of the hemostatic system indirectly, in unusual ways or milieu, resulting in confounding effects. It is not surprising therefore that the exact mechanism of action *in vivo* in man is mostly conjectural, though clinical consequences are often well understood.

The procoagulants range from activators of the extrinsic and intrinsic pathways to potent prothrombin converters, acting at the base of the common pathway. In the process of coagulation factor activation, other factors may be activated by downstream effects. This is particularly true for the prothrombin activators, as production of thrombin will often result in activation of factor XIII (clot stabilisation through cross linkage), plasminogen (fibrinolysis), tPA (plasminogen activation), antithrombin (thrombin inactivation), factors V and VIII (further thrombin production), protein C (inactivation of factors V and VIII), thrombomodulin (binding thrombin for interaction with antithrombin and protein C), and platelet effects, including potentially platelet activation. All of this will occur in a non-physiological environment, that is within free flowing blood rather than within the protected environment of a platelet plug. The prothrombin activators are, in general, the most clinically potent procoagulants, found in elapid and viperid venoms.

The clinical effect of prothrombin activators is defibrination. A similar effect

can be caused by direct fibrinogenolytic venom components, common in some viper venoms. They may selectively split the alpha or beta polypeptide chains off fibrinogen. However, there is no general activation of the coagulation system, as seen with prothrombin activators, and this generally limits their effect to pure defibrination. Clinically, however, events are rarely so simple, as most such venoms also contain other hemostatically active components such as the disintegrins, discussed earlier.

Some venoms, both elapid and viper, have true anticoagulant components that directly inhibit coagulation. The clinical role of these anticoagulants is, in general, uncertain.

Both elapid and viperid venoms may contain platelet active components. Some stimulate platelet aggregation, promoting thrombus formation *in vitro*, but with an unclear role clinically. Others inhibit platelet aggregation and may be important in the promotion of hemorrhage, such as the disintegrins discussed earlier. As such, they are clinically very important.

Nephrotoxins

A wide variety of elapid and viperid snakes can cause envenomation associated with renal damage or renal failure, and for some species (e.g. Russell's viper, *Vipera russelli*) it may be a dominant feature [42–44]. Mechanisms suggested for the pathophysiology of this renal failure are varied, including a direct venom toxin effect (*Vipera russelli*), venom-antibody complex deposition in the kidney, myoglobin damage to the kidney in cases with myolysis, deposition of products of coagulopathy in the kidney, renal hypotension secondary to envenomation related shock. It is possible that a number of different mechanisms may be involved in each case [45].

Others

Most snake venoms contain a rich array of substances, some of which are not classified above [46,47]. When considering the effects of the various venom components, it is important to understand that different enzymes may cause a release into the circulation of highly active endogenous substances. This may result in a spectrum of prominent and typical systemic effects. Substances like histamine, bradykinin, serotonin and prostaglandins may induce symptoms like profound hypotension, gastrointestinal hyperactivity, bronchospasm, facial oedema, etc. These are typical features of bites by some viperids.

EPIDEMIOLOGY

General

The collection of meaningful statistics on envenomation by any cause is generally poorly performed in most parts of the world, if such statistics are even collected. Thus the data available for evaluation of snakebite epidemiology

globally are very inadequate. The only global survey published (WHO) was a retrospective review of snakebite admissions and mortality, based on available government hospital statistics, for the period 1945 to 1949 [48]. This study estimated a total of 30–40,000 snakebite related deaths annually. A large number of these (20,000+) were from the Indian subcontinent. In this survey, only 9 snakebite deaths in 5 years were reported from Savanna West Africa. A more recent survey in rural areas of Nigeria suggested that for Savanna West Africa there were as many as 23,000 snakebite deaths each year [49]. While this very high figure has been questioned [50], it seems likely that the WHO survey results were a gross underestimate in some regions. A current figure of 100,000 snakebite deaths annually from India alone has been suggested to the authors by colleagues in India. though a more realistic figure would be 30,000–40,000. Figures from much of Asia and Africa are either not available, or suggest a continuing high incidence of snakebites. In Europe, the Americas and Australia, while the incidence of snakebites may be constant, death rates are falling. However, in the WHO study, these three areas were not major contributors to overall incidence or mortality, so the effect on global figures will be small. It seems probable that between 50,000 and 100,000 people die from snakebite each year, with probably more than 1,000,000 people bitten [51,52]. In some regions and nations snakebites and its direct and indirect costs are a major economic burden [53,54].

SYMPTOMATOLOGY

General effects

Clearly, a detailed discussion of all the effects of snakebites by all species is beyond the scope of this chapter. Salient points generally applicable will be covered. Firstly, it must be emphasised that for all venomous snakes there is a percentage of definite bites where no symptoms or signs of envenomation occur (the dry bite"). The percentage of dry bites will vary from species to species.

Should significant envenomation occur, problems caused may be local, systemic, or a combination of both. Nearly all viperid bites resulting in envenomation will have some evidence of a bite site, with fang puncture marks or scratches. Some elapid and most (fanged, venomous) colubrid snakes have small fangs and it is possible for them to deliver an effective bite with significant envenomation without leaving clearly visible fang puncture or scratch marks.

The onset of symptoms and signs of envenomation are highly variable, from minutes to many hours. Some centres consider a snakebite patient who is symptom free, to be out of the risk period only after 18 or even 24 hours. Some general symptoms and signs of significant (systemic) envenomation include headache, nausea, vomiting, abdominal pain, dizziness, blurred or double vision, impaired conscious state or collapse, fits. Envenomation may cause tachycardia, bradycardia, hypotension, or hypertension, depending on both the

snake and victim, and the phase of envenomation. Breathing difficulties such as bronchospasm may occur. Locally there may be swelling, blister formation and even hemorrhage following bites by snakes with locally active venom, such as most vipers and some cobras. However, life-threatening systemic envenomation can occur in the absence of any local effects following bites by many elapids and some vipers. The severity of envenomation may show considerable variation within a species, reflecting variation in the quantity of venom injected, location of the bite, age and weight of the victim, and the victim's physical activity immediately following the bite. Bites on the trunk, neck or head and in highly vascularised areas tend to be more serious. Small children and the elderly or infirm are at greater risk of severe envenomation. Physical activity after the bite accelerates venom absorption and often increases both the onset and severity of envenomation. Alcohol has a similar effect. Most patients bitten by a snake will be anxious and thus may have anxiety-mediated symptoms which can be confused with true envenomation.

Local tissue damage

Local tissue damage, including necrosis in some cases, is a major feature of envenomation by many snakes. The majority of vipers have this effect, as do some cobras in Africa and Asia, particularly the spitting species. For many of these snakes, the local effects and sequelae dominate the clinical picture of envenomation. Thus there may be skin damage, associated hemorrhage, underlying tissue damage and muscle myolysis, fluid loss into tissues (as for burns) resulting in hypotension and shock (which untreated may be lethal), vascular damage and secondary coagulopathy and hemolysis, both of which may result in kidney damage/failure, as may the shock. Extending vascular damage with increased permeability may result in pulmonary oedema, and in association with a coagulopathy, may precipitate cerebral hemorrhage. Local oedema may eventually involve the whole bitten limb and extend over the trunk and even involve other extremities. Maximal tissue damage may not be reached until 72 hours post bite.

Neurotoxic paralysis

Classic snakebite neurotoxic paralysis due to postsynaptic or presynaptic neurotoxins acting at the skeletal muscle neuromuscular junction has been well documented in association with elapid bites. However, not all elapid snakes cause paralysis, and there is clear experimental and clinical evidence that a variety of vipers also cause paralysis [17,40]. Postsynaptic neurotoxins tend to cause more rapid onset of paralysis than do the presynaptic neurotoxins, which usually have a latent period of one hour or more after binding to the neuromuscular junction. Thus paralysis symptoms and signs rarely occur in under 30 minutes of a bite and may take many hours before becoming apparent. Full paralysis involving even the diaphragm may take 24 hours or more to occur. Earliest effects of paralysis are usually seen in the face, where initially

there may be ptosis and decreased facial muscle expression, followed by progressive ophthalmoplegia, sometimes associated with fixed dilated pupils, dysarthria, and dysphagia. Then peripheral muscle weakness, weak intercostals and trunk muscles, and finally diaphragmatic paralysis will ensue. Not all cases will progress to this point. Breathing will finally cease when all muscles are paralysed, but respiratory difficulty is often apparent earlier, requiring assisted ventilation. Recovery from complete paralysis may be rapid, even without antivenom, in the case of some postsynaptically active venoms, but can be prolonged over days, weeks, or even months in the case of presynaptically active venoms, despite antivenom therapy.

Cardiovascular effects

The cardiovascular effects of envenomation may be secondary or primary, the latter being incompletely understood. Some cobras have cardiotoxins in their venom, which experimentally causes cardiac arrythmias and arrest, but the clinical relevance in man seems uncertain, as such effects are not documented. Some viper venoms may also have direct cardiac effects as well, again poorly understood. More important clinically are the secondary cardiac effects, due to venom-induced problems such as hypovolemic shock and hyperkalemia secondary to renal failure or massive myolysis. A variety of ECG changes have been reported following envenomation by diverse species of snakes. The circulatory shock seen following envenomation by many viperid species is multifactorial. There is loss of fluids from the vascular system, vasodilation and possibly some direct myocardial depression.

Hemorrhagic effects

As discussed earlier, the nature of venom induced hemorrhage is both multifactorial and incompletely understood. It is a feature of envenomation by many vipers and a few elapids. Classic features are bleeding gums and spontaneous skin hematomas. Hemoptysis, hematemesis, melaena and bleeding from the bite site are also suggestive of a hemorrhagin, but can equally occur if there is a major coagulopathy with defibrination, in the absence of a hemorrhagin. As with patients with coagulopathy, great care must be taken in choosing and performing invasive procedures, even venipuncture and insertion of lines. Anemia is a common sequelae of hemorrhagic envenomation, but may also occur if there is venom enzyme mediated hemolysis. This may be masked in the early phase of envenomation, because of hemoconcentration secondary to fluid loss into the bite area, as seen in some viperid bites.

Coagulopathy

The extent of coagulopathy will depend on the mechanism of induction utilised by the snake venom in question, the amount of venom injected, the rate and route of absorption, interaction with other venom induced effects, and the

prebite health of the patient. Thus, for bites by snakes with coagulopathic venom and sufficient venom injection to produce systemic envenomation, coagulopathy may range from very mild prolongation of prothrombin time, through to rapid complete defibrination or severe direct anticoagulation. At least in children bitten by Australian brown snakes, *Pseudonaja* spp., complete defibrination can occur in less than 30 minutes of the bite. At the other extreme, some vipers causing defibrination, such as the Malayan pit viper, *Calloselasma rhodostoma*, may have slow onset of coagulopathy, but continued release of depot venom over days, leading to a prolonged period of defibrination. The products of coagulopathy, such as fibrinogen breakdown products, which may reach very high plasma levels, are also anticoagulant and may potentially damage the kidneys. Renal failure may be associated with coagulopathy and so increase the depth of venom induced coagulopathy.

Clinically, most venom-induced coagulopathies are readily susceptible to appropriate antivenom therapy, and a snakebite-associated coagulopathy which fails to respond to otherwise adequate antivenom therapy, may indicate a secondary cause. Symptoms of coagulopathy are often few, such as persistent bleeding from the bite site or venipuncture sites. In a few severe cases there may be gastrointestinal or other bleeding, leading to hematemesis, melaena, hemoptysis, or hematuria. However, these are rare in uncomplicated coagulopathy, such as defibrination, being much more common in association with hemorrhagins. Any patient with impaired or absent coagulation function is at risk of bleeding, but unless there is a vascular breach, spontaneous bleeding is uncommon, except where there is also a hemorrhagin in the venom. Nevertheless, spontaneous cerebral bleeds do occur with normally benign snakebite defibrination. They are more likely if there has been a period of hypertension and drugs causing hypertension, should be used with great caution in this setting. In particular, adrenaline, if needed, is best given by intravenous infusion pump, so that low doses may be given and therapy quickly stopped. Venipuncture and line insertion should be limited to sites where bleeding can readily be controlled, therefore avoiding femoral venipunctures and subclavian central venous pressure line insertion.

Myolysis

Myolysis may be a local effect adjacent to the bite site, or a widespread systemic effect of venom, with sometimes severe generalised skeletal muscle destruction. Such destruction may take several hours to become clinically obvious, by which time damage is unlikely to be reversible by antivenom therapy. Symptoms include muscle pain, especially on movement or contraction against resistance, muscle weakness, thus mimicking paralysis, and dark red or brown urine, due to myoglobinuria. Red myoglobinuria looks like hematuria and will test positive for hemoglobin on dipstick testing, thus may be misdiagnosed as hematuria. There is a concomitant rise in plasma creatine kinase, which may reach levels of several 100,000 IU. In such cases of severe

myolysis there is likely to be muscle wasting. Complete recovery of muscle bulk over time can generally be expected if appropriate diet and physiotherapy are instituted during the recovery phase.

Renal effects

Only a few snake venoms have proven direct nephrotoxins causing kidney damage and failure, but many of these venoms have other components causing diverse effects likely to be detrimental to the kidney, such as shock and coagulopathy and the effect of hemorrhagins. For a wide array of other elapid and viper venoms, secondary kidney damage and failure are common sequelae of major systemic envenomation. Acute tubular necrosis is most commonly described, but there are cases of renal cortical necrosis, mainly following envenomation by vipers such as *Bothrops* spp., but also occasionally elapids.

Respiratory effects

The most important respiratory effect of snake envenomation is paralysis, as described earlier, but other problems do occur especially in viper bites, notably bronchospasm, mucous membrane swelling and pulmonary oedema.

Immunological effects

Bronchospasm and mucous membrane swelling — that may cause life-threatening airway obstruction — are seen in both children and adults, whereas pulmonary oedema occurs in small children with extensive local tissue damages and fluid shifts. All snake venoms are potentially immunogenic. Both early anaphylactoid and delayed reactions, such as serum sickness, may occur. The former is only likely in a repeated bite, usually seen in reptile keepers, where the reaction can be fatal. At least for some Australian elapid snakes, an early and sometimes profound lymphopenia occurs in cases with major envenomation. As this has not been researched for most non-Australian snakes, it is not known if this is a common accompaniment of snakebite envenomation by most species. Its causation is unknown. It is not associated with any observed increase in susceptibility to infection and remits spontaneously over a period of hours to days. An early leukocytosis is a common finding in patients with systemic envenomation.

FIRST AID

General principles

The first principle of first aid is to do the patient no harm. For most of the many first aid treatments for snakebite suggested over the years, this maxim

appears to have been ignored. The World Health Organisation and the International Programme on Chemical Safety convened a Working Group on Natural Toxins (WGONT) in 1989 which developed general guidelines for the management of all venomous bites and stings. This document, to be published within the INTOX project of WHO/IPCS, forms the basis of guidelines on both first aid and medical treatment recommended here.

Certain common forms of first aid for snakebite are now considered either useless, or more often, actually hazardous, and should not be used. Amongst these obsolete methods are: incision, suction by mouth, excision, use of topical chemicals (e.g. Condy's crystals), tourniquets, folklore medicines and patent cures, alcohol, vigorous exercise and electric shock treatment. The general recommendation of the WGONT was that immobilisation and elevation of the bitten limb using a splint and keeping the patient as inactive as possible were the only universally described applicable methods of first aid. Reassurance of the victim is most important. Two other methods of first aid were also considered and they are considered below.

Special cases

The pressure immobilisation method developed for Australian snakebite [55–57] was considered useful for bites by snakes which do not cause significant local tissue injury at the bite site. This applies to all dangerous snakes in Australia and New Guinea, as well as essentially neurotoxic species, such as the kraits (*Bungarus* spp.), some cobras (but not all), mambas (*Dendroaspis* spp.), coral snakes in Asia and the Americas, dangerous colubrids such as the boomslang and bird snake, and possibly a few vipers such as the south American rattlesnake, *Crotalus durissus terrificus*. For all of these snakes, except the Australian species, there is no substantial experimental or clinical evidence to show the safety of this method. However, based on both experimental and limited clinical work from Australia, the method does seem both safe and effective at delaying onset of major systemic envenomation [13,14,55–58]. Like all first aid for snakebite, it has the maximum chance of success if applied very promptly, and is unlikely to be effective if application is delayed more than 15 minutes. The method consists of application of a broad bandage over the bite site exerting moderate pressure, equated to about the pressure used in binding a sprained ankle. The bandage is extended to cover as much of the bitten limb as possible. The limb should be kept as still as possible during bandaging, then completely immobilised using a splint. If correctly applied, the bandage will not imperil limb blood supply and so may be left on for several hours if necessary, until the patient can be treated with antivenom, should this be indicated. The first aid does not destroy venom and so should be removed once the patient is in a hospital able to offer appropriate antivenom therapy. For the present this method of first aid is recommended for Australian snakebite. While not yet formally recommended for bites by the other snakes listed above, its use for bites by these snakes is probably both reasonable and worthwhile.

There is some recent research into the use of specially designed suction devices for removal of venom from the bite site following viper bite, particularly rattlesnake bite. Several commercial kits offering this are available. They mostly consist of a device to produce a small single or multiple incision over the bite area, and a suction apparatus will hopefully produce prolonged and powerful local suction over the incised area. As with the Australian method, they would need to be used very quickly after the bite, probably within a few minutes, and there appears to be great potential for increasing local tissue injury, introducing infection, and actually facilitating venom entry into the circulation. The evidence for their effectiveness seems equivocal at best [59,60]. At this time it is therefore not a recommended first aid.

MEDICAL MANAGEMENT

General approach to the envenomed patient

The management of snakebite is not as simple as giving antivenom to all those bitten. The effects of envenomation are many and complex and the unpredicted may and frequently does happen, occasionally with tragic consequences if those treating are not alert to all possibilities. No single chapter or textbook can substitute for clinical acumen and experience. A medical practitioner faced with managing a snakebite patient with major envenomation, with no experience of such treatment, would be well advised to seek the advice of a toxinologist expert in such cases, even if this means an international phone call. There are too many instances known to the authors, only a few published, where failure to consult an expert in snakebite management has had dire consequences for the patient and sometimes the physician as well.

All snakebites should be managed as a potential medical emergency. While a significant number of bites will not result in envenomation, this usually cannot be predicted reliably at the outset. If there is impending respiratory or cardiovascular failure, this clearly takes precedence in management, the ABC (airway, breathing, cardiac function) of treatment applying. A rapid initial assessment of extent of envenomation should be made. This should include measurement of vital function (pulse rate, blood pressure, respiratory rate, ECG, level of consciousness), estimation of intensity of any gastrointestinal symptoms, examination for evidence and extent of developing paralysis, myolysis, coagulopathy, metabolic disturbances, hematologic abnormalities including hemolysis and leucocytosis, and inspection of the bite area and measurement of limb diameter at and above the bite. In every patient showing evidence of systemic envenomation, a venous line should be inserted and blood taken for appropriate and available testing (see below). Urine output should be established early, if necessary using bladder catheterisation (avoid in children and in the tropics if possible). Providing adequate fluids can be given intravenously, then oral fluids should either be refused or restricted to clear fluids only.

A patient bitten by a dangerous snake may be apparently well and symptom free when first seen within a short time of the bite, especially if effective first aid has been used. Snakebite patients can deteriorate suddenly or gradually, but all must be carefully observed over about 24 hours for signs of envenomation. Nursing staff conducting regular assessment of an initially well patient should be instructed on specific signs to look for as evidence of envenomation, and not just left to do routine pulse and blood pressure.

Diagnosis of snakebite

The diagnosis of snakebite may be straightforward, as in the case of a reptile keeper bitten by a captive snake, or very difficult, as in the case of a child brought in *in extremis*, with no history of snakebite, and covered in dirt and scratches, obscuring possible bite sites. In the latter case the diagnosis of snakebite may be overlooked if a high index of suspicion is not maintained. A small child bitten by a dangerous snake will often not be able to give a history of snakebite and due both to small body size and activity after the bite, will often rapidly develop major systemic envenomation. This may manifest early as collapse and even convulsions following bites by some species, such as some Australian elapids, where local bite marks may be hard to find and local reaction is often absent. Similarly, for those snakes causing major local tissue injury and systemic vasodilation there may be rapid fluid shifts which, in a small child especially, may result in rapid development of hypotensive shock and collapse. A patient bitten by a species causing predominantly paralysis rather than local effects might present in the late stages of paralysis, virtually unable to move, unable to talk or give a history of snakebite, with respiratory difficulty, fixed dilated pupils, and unresponsive to painful stimuli (because of paralysis, though the patient may be fully conscious and all too aware of pain). This latter situation has great potential for tragic misdiagnosis and emphasises the need for suspicion of snakebite in a wide range of presentations.

Laboratory investigations and venom detection can be most useful in clarifying if the patient is suffering from snakebite and the extent of systemic abnormalities. However, in many situations and regions, neither are available and clinical assessment remains paramount.

Venom detection

The detection of snake venom from bite site swabs, urine or plasma is a most valuable way of both confirming that a snakebite has occurred, and documenting the type of snake and indicating the possible extent of envenomation. The use of ELISA methods for venom detection has been described for a number of years [50,61], but for most regions it is either not available at present, or only as a research tool. In Australia there is a commercial venom detection kit, using an ELISA method, and sensitive to nanogram quantities of venom from the bite site or in urine (unreliable in testing plasma). Within 12 minutes it can qualitatively indicate both the presence of snake venom and the species group of snake, allowing use of specific antivenom if indicated. It has proved a useful

tool clinically and for epidemiological studies [62–66]. A quantitative venom assay would be even more useful in studying snakebite, though caution should be exercised in interpreting plasma venom levels in relation to clinical extent of envenomation. Studies undertaken in patients bitten by European vipers have shown a good correlation between clinical signs and the level of venom antigens in blood and urine [67,68].

Laboratory investigations

Apart from venom detection, a wide variety of laboratory investigations can be useful in assessing snakebite patients, the pattern of investigations depending on the type of snake and the clinical picture. Full blood count/examination (all cases), coagulation studies (coagulopathy/hemorrhage), creatine kinase (myolysis), electrolytes (all cases), renal function (all cases), and acid base balance (all cases) are the most commonly indicated investigations. Even if initially normal, repeat studies in a few hours are often advisable. For bites by species causing defibrination coagulopathy, serial studies are needed. At least for some such snake species (e.g. Malayan pit viper, *Calloselasma rhodostoma*), release of depot venom may cause recurrent coagulopathy up to 72 hours post bite, despite initial antivenom therapy. Urine should be checked for output volume, standard ward (dipstick) testing, and myoglobin if appropriate. Detailed discussion of laboratory findings in envenomation by particular snake species is beyond the scope of this chapter.

If laboratory facilities are not readily available, a simple bedside assessment of clotting function can be made using whole blood clotting time in a glass test tube.

General and symptomatic treatment

For comments on the immediate assessment of the envenomed patient, refer to the section "General approach to the envenomed patient". In most cases the patient should have an intravenous line inserted and intravenous fluid administered at maintenance level plus replacement of documented or expected losses with appropriate fluids (e.g. in cases with hypotensive shock due to local tissue damage and fluid shift). Approaches to the choice of intravenous fluid used in treating shock vary between hospitals and countries, both crystalloids and colloids having favour in particular centres. Fluid replacement should be accompanied by careful measurement of fluid and electrolyte balance. Avoid over hydration and hemodilution problems, especially in children, where electrolyte imbalance may occur. Inotropic support and vasoactive drugs may also be required in the treatment of severe hypotension. Alkalinisation of the urine is recommended in the presence of hemolysis or myolysis. Anaphylactoid reactions such as angioneurotic oedema, bronchospasm, and sudden hypotension may be managed with adrenaline, either as a controlled intravenous infusion using an infusion pump, or by subcutaneous injection (avoid intramuscular route if there is a coagulopathy). There is no convincing support for the efficacy of corticosteroids in counteracting the toxic effects of snake venoms. However corticosteroids may have a role in the treatment and prophylaxis of

delayed hypersensitivity reactions to venom (and antivenom). Pain relief may be necessary, using the least hazardous drugs compatible with adequate analgesia. Avoid respiratory depressant narcotics if possible. In most cases, especially those likely to have a coagulopathy/hemorrhagic diathesis, avoid aspirin or similar drugs inhibiting platelet function. Ensure tetanus prophylaxis and treat with antibiotics only if infection occurs or there is a strong clinical probability of infection developing.

Antivenoms

Antivenoms remain the most important treatment of systemic snakebite envenomation. They are specific antidotes and often the only treatment which will have any chance of reversing the venom effects. The value of antivenom in reducing the local damage caused by some venoms is less clear, but when given, it is, in some types of envenomation, most likely to prevent further development of local symptoms [69]. A disadvantage of most existing antivenoms is the risk of untoward reactions. Most current commercial snake antivenoms are hyperimmune horse sera, refined to a variable extent, depending on manufacturer. Thus some remain essentially crude horse serum, while others are highly refined specific Fab'_2 or even Fab fragments. All horse serum products have some potential for stimulating both immediate and delayed hypersensitivity reactions and causing complement activation. The more refined the product, the safer it is likely to be.

Currently there are several approaches to improving the safety of antivenoms. One method is affinity chromatography of Fab fragments, resulting in only antibodies specific for the snake venom. Another approach is use of another antibody source, such as sheep (the serum of which appears to cause far less hypersensitivity reactions in man than horse serum), and again the application of high refining including affinity chromatography of Fab fragments [70]. It is too early to state that these new antivenoms will be more effective and safer, but initial experience with early trials is very encouraging [71]. These new sheep serum-based antivenoms are available, or under development, for European viper bites, North American crotalid bites, Nigerian *Echis* bites, Sri Lankan *Vipera russelli* bites, and Australian elapid bites (Therapeutic Antibodies Inc., personal communication).

As currently available, snake antivenoms should be considered as potentially dangerous and usually very expensive antidotes to snakebite envenomation. They are normally the treatment of choice for systemic envenomation, but should only be used if there is significant systemic or local envenomation. It is advisable for centres holding antivenom to define criteria for antivenom use for each snake species. Antivenom should never be given to a patient exhibiting neither of the above. Wherever possible an antivenom specific for the species of snake involved should be used rather than a polyvalent product covering a variety of species including the target species. Do not use antivenom not proven potent for the particular snake involved. Ensure the antivenom is current, has been stored appropriately, and is free of contamination if liquid (i.e. not cloudy).

Use a dose appropriate for the snake species and clinical extent of envenomation. Children need the same dose as adults. Be prepared to give further doses if necessary. A common mistake is to give too little antivenom. In the case of coagulopathy it may be possible to titrate antivenom dosage against resolution of the coagulopathy as indicated in serial coagulation tests. Guidelines on the quantity of antivenom to use are beyond the scope of this chapter, but in most cases the manufacturer will include such information with the antivenom.

One common scheme used in North America for Wyeth Polyvalent (Crotalidae) Antivenom is based on a four-tier grading. The first grade is no evidence of local or systemic envenomation, not requiring antivenom. The second grade is minimal envenomation, with mild local effects only, limited to the area adjacent to the bite site, without systemic envenomation, requiring about 5–8 vials of antivenom. The third grade is moderate, characterised by tissue damage extending beyond the immediate bite area and systemic envenomation signs and symptoms and associated moderate changes in laboratory parameters (e.g. thrombocytopenia, hypofibrinogenemia), requiring about 8-12 vials of antivenom. Frequent measurement of limb circumference at the bite site and 10 cm and 20 cm proximal to the bite may assist in quantifying the development of local venom induced damage and worsening of the grade of envenomation. The fourth grade, severe, is characterised by extensive tissue damage involving the whole bitten limb, with marked signs and symptoms of systemic envenomation and more severe laboratory test abnormalities, requiring 12–30 vials of antivenom. However, all such schemes are guidelines only and in major envenomation one should always be prepared to give further antivenom.

Antivenom for snakebites is almost always most effective if given intravenously. Other routes such as intramuscular are too slow and injection into and around the bite site is both ineffective and dangerous. Due to the potential for immediate hypersensitivity reactions, antivenom should be given by a health professional able to treat such a complication with appropriate drugs ready to hand, particularly adrenaline. Whenever possible it is best to dilute the antivenom for intravenously infusion, starting very slowly and increasing the rate if no reaction occurs. However one study has shown that intravenous push injection of antivenom may not have a significantly higher chance of reactions, an important consideration in regions where intravenous infusions are either not possible or too expensive [72]. Again, if possible, an infusion pump with diluted adrenaline should be connected to the intravenous line so that rapid and controlled adrenaline can be immediately given to control hypotension or bronchospasm should they occur. Though still widely used, skin pretesting with antivenom to check for allergy is not recommended as it is both hazardous, time wasting, and non-diagnostic with common false positive and false negative results [66]. Similarly the use of premedication prior to antivenom is unproven and of doubtful value [57]. The use of adrenaline as premedication is potentially very hazardous, particularly if the patient has a coagulopathy/hemorrhagic diathesis.

Any patient who has received antivenom therapy is at risk of delayed reactions, notably serum sickness. As this may be mistaken for a viral illness

by the patient, it is important that every patient given antivenom be told about serum sickness prior to discharge, so that they will return for treatment should any relevant symptomatology occur. Patients receiving more than 50 ml of intravenous horse serum antivenom are at a significant risk of serum sickness and it is worth considering a short prophylactic course of oral steroids commencing after completion of antivenom therapy.

A listing of most currently available antivenoms for bites by each species or group of species of venomous snakes is given in Table 33.1, with indexing to manufacturers in Table 33.2, at the end of this chapter. This listing is based on a recently published work [93] which surveyed antivenom availability worldwide. However, the details for each snake or group of snakes is derived from a variety of sources, and is in some cases a best guess approximation, where clinical information is either scant or lacking. Therefore, the information in Table 33.1 should be used as a starting guide only. Not all specimens of a given species of snake have exactly the same mix of venom components and clinical manifestations may vary. Readers who actually treat snakebites, are invited to send details of non-listed or different clinical effects for updating these tables.

Treatment of specific complications

Local tissue injury

A variety of surgical interventions have been tried in an attempt to limit local tissue injury following snakebites, especially viper bites such as rattlesnake bites in North America. However most studies showed that early surgical intervention is most likely either to have no benefit or to actually extend the area of damage and prolong hospitalisation. It was common practice to perform fasciotomies on bitten limbs with early swelling in response to envenomation. The theory was that oedema would compromise vascular supply to either the limb or one limb compartment, causing further damage. Careful clinical studies have shown that where compartment pressure is measured in cases with major oedema, there may be low pressure with no threat of compartment syndrome, and the tissue damage caused by fasciotomy often increases scarring and long-term functional deficits [51,73]. It is therefore recommended that fasciotomy is performed as a last resort only when there is clear evidence of vascular damage or compartment syndrome (demonstrated by measurement of intra-compartmental pressure).

Snakebites causing extensive local reactions, particularly some cobra bites, may ultimately produce local necrosis requiring surgical debridement and even skin grafting. In general, all such surgical intervention should be delayed at least 24 hours from the time of the bite, often considerably longer. Unless there has been external breach of the skin by either first aid or surgery, local infection is uncommon, but should always be considered and treated as necessary with antibiotics.

Paralysis

Neurotoxin-mediated paralysis is best treated in the early stages with appropriate antivenom therapy, as the more established and severe the paralysis is at the onset of treatment, the less likely it is that antivenom will completely reverse the paralysis. This is especially true of snakebites by species containing presynaptic neurotoxins in their venom. Providing the venom contains only postsynaptic neurotoxins it is sometimes possible to reverse paralysis using anticholinesterases (such as edrophonium or neostigmine) [74–76]. However, this should not be considered an alternative to antivenom treatment, but merely an adjunct or emergency measure should antivenom be unavailable. The potential secondary complications of maintaining a patient on a ventilator for complete paralysis are such that this is truly the final resort in managing snakebite-induced paralysis. It should never be considered an alternative to antivenom therapy.

Myolysis

Given that muscle damage may occur well before clinical signs and elevation of creatine kinase or myoglobinuria occur, it will often not be possible to reverse myolysis with antivenom therapy. Thus treatment will largely be directed towards supportive therapy and prevention of secondary effects such as hyperkalemia and renal failure. Adequate intravenous hydration and renal throughput, alkalinisation of the urine, and in the later stages, physiotherapy and a high-protein diet may all be useful.

Coagulopathy

The management of snakebite coagulopathy has been controversial and remains confusing, not least because of the many different ways venom may affect hemostasis. The recommendations made here should be taken as general guidelines and may not be applicable for every species of venomous snake. Because the action of venom in causing coagulopathy is within the bloodstream, it is most readily accessible to antivenom. If available, specific antivenom capable of neutralising the venom is the most efficacious treatment and should be used without delay. The dose required depends on many factors, but may be several times the manufacturer's minimum recommended dose. It is generally unwise to give factor replacement therapy before venom has been neutralised by antivenom, except when there is catastrophic hemorrhage requiring very urgent reversal, in which case large amounts of both factor replacement and antivenom should be given very rapidly. The use of heparin to counteract coagulopathy is generally an unsound treatment, both on experimental and clinical grounds [57].

Renal failure

The best treatment for renal failure secondary to snakebite is to avoid it whenever possible by ensuring adequate hydration and cardiovascular function. The management of established renal failure is essentially the same whatever the cause.

Table 32.1. *Consolidated information on taxonomy, distribution, lethality, venom effects, first aid and antivenom for all dangerous venomous snakes, by family, genus, and for some by species [4,5,7–10,15,17,21,22,40,41,43,47,51,58,65,74–93]*

Key:

SNAKE = Family and an accepted common name (other common names may also exist).

SCIENTIFIC NAME = Generally accepted scientific name (other names may also occur in the literature).

DISTRIBUTION = Generally accepted distribution, by name of country, or by region or continent; E = Europe; Af = Africa; NAf = northern Africa; SAf = southern Africa; ME = Middle East; NAm = North America; CAm = Central America; SAm = South America; Aust = Australia; NG = New Guinea; Ind = Indonesia (or part thereof); SEA = south east Asia; SWA = south west Asia; Ind = Indian subcontinent (includes Sri Lanka); Ch = China; Jap = Japan; Tai = Taiwan.

LETHALITY = Generally accepted severity of confirmed bite in humans; Sev = severe (often potentially lethal); Mod = moderate (bites often cause significant envenoming, sometimes potentially lethal); Mild = mild (most bites cause only minor envenomation, generally not likely to be lethal); ? = clinical information on severity either lacking or conflicting.

VENOM EFFECTS = Generally accepted clinical effects of venom in man, where known; ? = considerable uncertainty or lack of information on effect(s); A = cardiotoxic; C = coagulopathy; E = hemolysis; G = local tissue necrosis; H = haemorrhagic; L = local tissue swelling/blisters/hemorrhage/ damage; M = myolysis; N = neurotoxic paralysis; P = antiplatelet actions; R = renal damage/failure; S = shock; W = anticoagulant.

FIRST AID = Generally accepted method recommended for first aid; I = immobilisation; BI = pressure bandage and immobilisation (Australian method for snakes which do not cause significant local tissue damage).

ANTIVENOM = Possible antivenoms that may be used in treating envenomation. These are not listed necessarily in order of preference. Numbers refer to individual antivenoms listed in Table 32.2. NA = no antivenom available.

**Note:*

For all information in this Table please note that clinical and venom data represent a synthesis of published information available to the authors. For many species listed, there is little such information available. Individual medical practitioners may have extensive but unpublished experience of bites by various species of snakes which may not agree with the information given here. Should this be the case, we cordially invite these colleagues to write to us detailing this new information. We will incorporate it in our management protocols and future editions of this publication, with full aknowledgement of source.

Snake	Scientific name	Distribution	Lethality	Venom effects	First aid	Antivenom
Family Colubridae						
Brown tree snake	*Boiga irregularis*	Australia, NG, Guam	Low (? Mod in infants)	L, ? N	BI	NA
Boomslang	*Dispholidus typus*	SubSaharan Africa	Mod to Sev	C, H, R	BI	8 (M)
Argentine blackheaded snake	*Elapomorphus bilineatus*	South America	Mod	H, C	BI	NA

Montpelier snake	*Malpolon monspessulanus*	Mediterranean, ME	Mild to Mod	L, ? N	BI	NA
Red necked keelback	*Rhabdophis subminiatus*	SE Asia, Japan, China	Mod	L, C, H, R	BI	112 (M)
Yamakagashi	*Rhabdophis tigrinus*	Japan	Mod	L, C, H, R	BI	112 (M)
Bird snakes	*Thelatornis spp.*	Southern Africa	Mod to Sev	H, C, R	BI	NA
Culebra de cola corta	*Tachymenis peruviana*	South America	Mild to Mod	L, H, C	BI	NA
Family Elapidae						
Death adders	*Acanthophis spp.*	Australia, NG, Indo	Sev	N	BI	151 (M), 156 (P)
African coral snakes	*Aspidelaps spp.*	Southern Africa	Mild, occ. deaths	N	BI	NA
Australian copperheads	*Austrelaps spp.*	Australia	Sev	N, W	BI	157 (M), 156 (P)
Water cobras	*Boulengerina spp.*	Central Africa	? Mild	? N	BI	NA
Kraits	*Bungarus spp.*	East Asia	Sev	N	BI	80 (P)
	Bungarus caeruleus		Sev	N	BI	67 (P), 70 (M), 73 (P), 74 (M), 78 (P)
	Bungarus ceylonicus	Sri Lanka	Sev	N	BI	78 (P)
	Bungarus fasciatus		Sev	N	BI	67 (P), 78 (P), 80 (P), 91 (M), 95 (P), 97 (M), 103 (M)
	Bungarus multicinctus		Sev	N	BI	100 (P), 107 (M)
Asian coral snakes	*Calliophis spp.*	East Asia	Mild	?	BI	NA
Australian whip snakes	*Demansia spp.*	Australia, NG	Mild	?N	BI	NA (try 157)
Mambas	*Dendroaspis spp.*	Southern Africa	Mod to Sev	N	BI	119 (P)
	Dendroaspis angusticeps		Mod to Sev	N	BI	6 (P), 9 (P), 122 (P)
	Dendroaspis jamesoni		Mod to Sev	N	BI	6 (P), 9 (P), 122 (P)
	Dendroaspis polylepis		Sev	N	BI	6 (P), 9 (P), 122 (P), 128 (P)
	Dendroaspis viridis		Mod	N	BI	6 (P), 122 (P), 128 (P)
African garter snakes	*Elapsoidea spp.*	Southern Africa	Mild	L	I	NA
Rinkhals spitting cobra	*Hemachatus haemachatus*	Southern Africa	Mod	L, ? N, spits	BI	6 (P), 10 (P), 118 (P), 128 (P)

***Table 32.1** continued*

Snake	Scientific name	Distribution	Lethality	Venom effects	First aid	Antivenom
Broad headed snakes	*Hoplocephalus spp.*	Australia	Mild	? N	BI	157 (M)
Asian coral snakes	*Maticora spp.*	East Asia	Mild, ? fatalities	? N	BI	NA
Small eyed snake	*Micropechis ikaheka*	New Guinea	Mod to Sev	? N	BI	NA
American coral snake	*Micruroides euryxanthus*	SAm, CAm	Mod, occ.deaths	N	BI	12 (M)
American coral snakes	*Micrurus spp.*	CAm, SAm	Mod, occ deaths	N	BI	53 (P), 22 (P), 20 (P), 23 (M), 32 (P), 50 (P), 44 (P), 12 (M)
Chinese cobra	*Naja atra (N.n.atra)*	SE China	Mod	N	BI	100 (P), 102 (M)
Egyptian cobra	*Naja haje*	Africa, ME	Mod to Sev	N	BI	5 (P), 6 (P), 118 (P), 119 (P), 120 (P), 127 (P), 128 (P), 129 (P)
Monocled cobra	*Naja kaouthia*	SE Asia	Sev	L, N	BI	69 (M), 85 (P), 86 (M), 89 (M), 90 (M), 121 (M)
Forest cobra	*Naja melanoleuca*	Central to South Africa	Mod to Sev	N	I	6 (P), 118 (P), 119 (P), 127 (P), 128 (P)
Mozambique spitting cobra	*Naja mossambica*	Southern Africa	Mod	L, G, spits	I	6 (P)
Indian cobra	*Naja naja (N.n.naja)*	India, adjacent areas	Sev	N, ? A	BI	6 (P), 67 (P), 68 (P), 69 (M), 73 (P), 75 (M), 78 (P), 80 (P), 81 (M), 120 (P), 129 (P), 128 (P), 144 (M), 146 (P), 147 (P)
Black necked spitting cobra	*Naja nigricolis*	Africa	Sev	L, G, H, ? A	I	6 (P), 118 (P), 119 (P), 127 (P), 128 (P)
Cape cobra	*Naja nivea*	Southern Africa	Sev	N	BI	6 (P), 10 (P), 118 (P), 128 (P)
West Asian cobra	*Naja oxiana (N.n.oxiana)*	SE Asia	Mod to Sev	L, G, occN, ? A		60 (P), 61 (P), 142 (M)

Philippines cobra	*Naja philippinensis (N.n.p.)*	Philippines	Sev	L, N	BI	99 (M)
Malayan spitting cobra	*Naja sputatrix (N.n.sputatrix)*	SE Asia	Mod to Sev	L, G, occN, ? A, spits	I	89 (M), 95 (P), 98 (M), 131 (M)
Samatran cobra	*Naja sumatrana (N.n.s.)*	SE Asia	Mod to Sev	L, G, occN, ? A		89 (M), 95 (P), 98 (M), 131 (M)
Australian tiger snakes	*Notechis spp.*	Australia	Sev	N, C, M, N, occ L	BI	157 (M), 156 (P)
King cobra	*Ophiophagus hanna*	SE Asia	Sev	L, N, ? A	I, ? BI	6 (P), 67 (P), 78 (P), 89 (M), 90 (M)
Taipans	*Oxyuranus spp.*	Australia, NG	Sev	N, C, M, R, H in NG	BI	153 (M), 156 (P)
Burrowing cobra	*Paranaja multifasciata*	Africa	?	?	BI	NA
Mulga snake	*Pseudechis australis*	Australia, NG	Sev	M, R, ? W, L	BI	155 (M), 156 (P)
Spotted mulga snake	*Pseudechis butleri*	Australia	? Sev	? (M, R, ? W, L)	BI	155 (M), 156 (P)
Colletts snake	*Pseudechis colletti*	Australia	Mild to Mod	M, L	BI	157 (M), 155 (M), 156 (P)
Spotted black snake	*Pseudechis guttatus*	Australia	Mild to Mod	M, L	BI	157 (M), 155 (M), 156 (P)
Red bellied black snake	*Pseudechis porphyriacus*	Australia	Mild to Mod	L, E	BI	157 (M), 155 (M), 156 (P)
Papuan black snake	*Pseudechis papuanus*	New Guinea	Mod to Sev	C, ? H	BI	155 (M), 156 (P)
Tree cobras	*Pseudohaje spp.*	Africa	?	?	BI	6 (P)
Australian brown snakes	*Pseudonaja spp.*	Australia, NG	Sev	C, R, N	BI	158 (M), 156 (P)
Rough scaled snake	*Tropidechis carinatus*	Australia	Mod to Sev	N, C, M, R	BI	157 (M), 156 (P)
Desert black snake	*Walterinnesia aegyptia*	ME, NAf	Mod	N	BI	6 (P), 58 (M)
Family Hydrophiidae						
Subfamily Hydrophiinae						
Horned sea snake	*Acalyptophis peronii*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Sea snakes	*Aipysurus spp.*	Indo-Pacific Ocean	Mod	? M	BI	152 (P)

***Table 32.1** continued*

Snake	Scientific name	Distribution	Lethality	Venom effects	First aid	Antivenom
Olive sea snake	*Aipysurus laevis*	Indo-Pacific Ocean	Mod	N	BI	152 (P)
Stokes sea snake	*Astrotia stokesii*	Indo-Pacific Ocean	Sev	N	BI	152 (P)
Turtle headed seasnakes	*Emydocephalus annulatus*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Beaked sea snake	*Enhydrina schistosa*	Indo-Pacific Ocean	Sev	M	BI	152 (P)
Mangrove seasnake	*Ephalophis greyi*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Black ringed mangrove seasnake	*Hydrelaps darwiniensis*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Banded seasnakes	*Hydrophis spp.*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Spine bellied seasnake	*Lapemis hardwickii*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Northern mangrove seasnake	*Parahydrophis mertoni*	Indo-Pacific Ocean	Mild	? M	BI	152 (P)
Yellow bellied seasnake	*Pelamis platurus*	Indo-Pacific Ocean	Mod	N	BI	152 (P)
Subfamily Laticaudinae						
Sea kraits	*Laticauda spp.*	Indo-Pacific Ocean	Mod	N	BI	152 (P)
Family Atractaspidae						
Mole vipers	*Atractaspis spp.*	Africa, ME	Mod to Sev	L, A, ? N	I	NA
Family Viperidae						
Subfamily Viperinae						
Bush vipers	*Atheris spp.*	Africa	Mild	?	BI	NA
Puff adder	*Bitis arietans*	Africa	Sev	L, G, H, R, S	I	6 (P), 10 (P), 118 (P), 119 (P), 127 (P), 128 (P)
Mountain adder	*Bitis atropos*	Africa	Mild	N	BI	? as for Puff Adder above
Horned adder	*Bitis caudalis*	Africa	Mild	L, G	I	? as for Puff Adder above

Many horned adder	*Bitis cornuta*	Africa	Mild	L, G	I	? as for Puff Adder above
Gaboon viper	*Bitis gabonica*	Africa	Sev	L, G, H, C, R, S, A	I	6 (P), 10 (P), 118 (P), 119 (P), 127 (P), 128 (P)
	Bitis heraldica	Africa	? Mild	? L	I	? as for Puff Adder above
Rhinoceros viper	*Bitis nasicornis*	Africa	Sev	L, G, H, R, S	I	6 (P), 118 (P), 128 (P)
Peringueys viper	*Bitis peringueyi*	Africa	Mild	L	I	? as for Puff Adder above
Dwarf adder	*Bitis schneideri*	Africa	Mild	L	I	? as for Puff Adder above
	Bitis worthingtoni	Africa	? Mild	N	I	? as for Puff Adder above
Desert Mountain adder	*Bitis xeropaga*	Africa	? Mild	? L	I	? as for Puff Adder above
Night adders	*Causus spp.*	Africa	Mild	L, ? N	I	6 (P)
Horned viper	*Cerastes spp.*	N. Africa	Mod	L, C	I	1 (P), 2 (P), 3 (P), 4 (P), 5 (P), 7 (M), 60 (P), 127 (P), 129 (P), 148 (P), 7 (M), 120 (P)
Carpet viper	*Echis spp.*	Africa, ME, Ind	Sev	L, G, C, H, R, S	I	7 (M), 55 (M), 57 (M), 60 (P), 62 (P), 67 (P), 72 (M), 73 (P), 77 (M), 78 (P), 79 (P), 80 (P), 84 (M), 118 (P), 119 (P), 120 (P), 127 (P), 129 (P), 140 (P), 143 (P), 146 (P)
Horned viper	*Pseudocerastes spp.*	ME, WA	Mod to Sev	? N	BI	60 (P), 63 (P), 64 (M)
Long nosed viper	*Vipera ammodytes*	SE Europe, WA	Mod to Sev	L, N	BI	117 (P), 123 (P), 124 (P), 125 (P), 126 (M), 132 (P), 134 (M), 135 (M), 148(P), 149 (P), 150 (M)

***Table 32.1** continued*

Snake	Scientific name	Distribution	Lethality	Venom effects	First aid	Antivenom
Asp	*Vipera aspis*	Europe	Mod	L, H, S	I	117 (P), 123 (P), 124 (P), 125 (P), 126 (M), 132 (P), 134 (M), 135 (M), 148 (P), 149 (P), 150 (M)
European viper	*Vipera berus*	Europe	Mod	L, H, S	I	117 (P), 123 (P), 124 (P), 125 (P), 126 (M), 132 (P), 134 (M), 135 (M), 148 (P), 149 (P), 139 (M), 150 (M)
	Vipera cerastes	? WA, ME	?	?	I	60 (P)
Caucasus viper	*Vipera kasnakovi*	Russia	? Mild	? L, H, S	I	126 (M), 148 (P), 149 (P), 150 (M)
Latastes viper	*Vipera latasti*	Iberia, NAf	Mod	L, H, S	I	126 (M), 148 (P), 149 (P), 150 (M)
	Vipera latifi	ME	Mod	L, H, S	I	63 (P), 64 (M), 65 (M), 148 (P)
Blunt nosed viper	*Vipera lebetina*	ME, WA	Mod	L, H, S	I	1 (P), 2 (P), 3 (P), 60 (P), 63 (M), 64 (M), 80 (P), 120 (P), 126 (M), 127 (P), 129 (P), 134 (M), 140 (P), 141 (M), 145 (M), 147 (P), 148 (P)
	Vipera meridionalis	Europe, ME	Mod to Sev	L, H, S, ? N	I	134 (M)
	Vipera mesocoronis	Europe	Mild to Mod	L, S, H	I	134 (M)
Palestine viper	*Vipera palaestinae*	ME	Mod	L, H, S	I	56 (M), 59 (M), 120 (P), 126 (M), 129 (P), 148 (P)
Russells viper	*Vipera russelli*	Ind to SE Asia	Sev	L, G, H, C, M, R, S	I	67 (P), 68 (P), 71 (M), 73 (P), 76 (M), 78 (P), 79 (P), 80 (P), 83 (M), 85 (P), 87 (M), 92 (M)

	Vipera seoanei	Spain	? Mild to Mod	L, S, H	I	148 (P), 149 (P), 150 (M)
Meadow viper	*Vipera ursinii*	Europe, WA	Mild	? L, H, S	I	126 (M), 132 (P), 134 (M), 148 (P), 149 (P), 150 (M)
	Vipera xanthina	Europe, WA	Mild	L, H, S	I	60 (P), 126 (M), 129 (P), 134 (M), 148 (P)
Subfamily Crotalinae						
Cantil	*Agkistrodon bilineatus*	CAm	Mild to Mod	L, S, G, H	I	13 (P), 21 (P)
Mamushi	*Agkistrodon blomhoffii*	Russia, China, Japan	Mild to Mod	L, S, G, H	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)
Dusky mamushi	*Agkistrodon caliginosus*	Korea	Mild to Mod	L, S, G, H	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)
American copperhead	*Agkistrodon contortrix*	NAm	Mod	L, S, G, H, C	I	11(P)
Karaganda pit viper	*Agkistrodon halys*	Russia, China	Mild to Mod	L, S	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)
Himalayan pit viper	*Agkistrodon himalayanus*	Himalayas	? Mod	? L, S	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)
Central Asian pit viper	*Agkistrodon intermedius*	Russia, China	? Mod	? L, S	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)
Likiang pit viper	*Agkistrodon monticola*	China	? Mod	? L, S	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)

***Table 32.1** continued*

Snake	Scientific name	Distribution	Lethality	Venom effects	First aid	Antivenom
Cottonmouth	*Agkistrodon piscivorus*	NAm	Mild to Mod	L, S, G, H	I	11 (P)
Tibetan pit viper	*Agkistrodon stauchi*	Tibet, China	? Mod	? L, S	I	60 (P), 66 (M), 105 (M), 109 (M), 110 (M), 111 (M), 113 (M), 114 (M), 115 (M)
Palm pit viper	*Bothriechis spp.*	CAm	Mild	L, G	I	21 (P)
Eyelash palm pit viper	*Bothriechis schlegelii*	CAm	Mod	L, G	I	21 (P)
Forest pit viper	*Bothriopsis spp.*	CAm, SAm	Mild to Mod	L, G	I	40 (P)
Chocoan pit viper	*Bothriopsis punctata*	SAm	Mod to Sev	L, G, ? (C, H, M, R)	I	40 (P)
Lanceheads	*Bothrops spp.*	CAm, SAm	Mod to Sev	L, G, C, H, M, P, R	I	11 (P), 43 (P), 52 (P), 35 (P), 38 (P), 18 (P)
Urutu	*Bothrops alternatus*	SAm	Mod	L, G	I	29 (P), 30 (P), 31 (P), 33 (P), 36 (P), 47 (P), 48 (P), 51 (P)
Patagonian lancehead	*Bothrops ammodytoides*	SAm	Mod	L, G	I	47 (P)
Terciopelo	*Bothrops asper*	SAm	Sev	L, G	I	13 (P), 14 (M), 16 (P), 21 (P), 25 (M), 26 (P), 43 (P)
Common lancehead	*Bothrops atrox*	SAm	Sev	L, G	I	11 (P), 14 (M), 16 (P), 18 (P), 19 (P), 21 (P), 39 (P), 40 (P), 43 (P)
Brazils lancehead	*Bothrops brazili*	SAm	Mod	L, G	I	40 (P)
Saint Lucia lancehead	*Bothrops caribbaeus*	SAm	Sev	L, G	I	? as for common lancehead above
Cotiara	*Bothrops cotiara*	SAm	? Mod	? L, G	I	29 (P), 30 (P), 31 (P), 33 (P)
Golden lancehead	*Bothrops insularis*	SAm	Sev	L, G	I	? as for common lancehead above
Jararaca	*Bothrops jararaca*	SAm	Sev	L, G, C, H, M, R	I	29 (P), 30 (P), 31 (P), 33 (P), 36 (P), 48 (P)

Jararacussu	*Bothrops jararacussu*	SAm	Sev	L, G, C, H, M, R	I	29 (P), 30 (P), 31 (P), 33 (P), 36 (P), 48 (P)
Fer de lance	*Bothrops lanceolatus*	Martinique	Sev	L, G	I	? 11 (P), 18 (P)
Brazilian lancehead	*Bothrops moojeni*	SAm	Sev	L, G	I	29 (P), 30 (P), 31 (P), 33 (P), 36 (P)
Neuwieds lancehead	*Bothrops neuwiedi*	SAm	Sev	L, G	I	29 (P), 30 (P), 31 (P), 33 (P), 36 (P), 48 (P), 51 (P)
Desert lancehead	*Bothrops pictus*	SAm	Sev	L, G	I	40 (P)
Malayan pit viper	*Calloselasma rhodostoma*	SEAsia	Mod to Sev	L, G, H, C, R, S	I	93 (M), 94 (M), 95 (P), 96 (M), 130 (M)
Rattlesnakes	*Crotalus spp.*	NAm, CAm, SAm	Mild to sev	L, G, C, H, E, P, M, N, R	I	11 (P), 35 (P), 17 (P)
Western diamondback RS	*Crotalus atrox*	NAm, CAm	Sev	L, G, S, C	I	11 (P), 13 (P), 15 (P), 16 (P)
Eastern diamondback RS	*Crotalus adamanteus*	NAm	Sev	L, G, S,	I	11 (P)
Mexican westcoast RS	*Crotalus basiliscus*	CAm	Sev	L, G, S	I	11 (P)
Sidewinder	*Crotalus cerastes*	NAm, CAm	Mod	L, G	I	11 (P)
Cascabel, neotropical RS	*Crotalus durissus durissus*	CAm, SAm	Mod	L, G, S	I	13 (P)
Cascabel, neotropical RS	*Crotalus d. terrificus*	SAm	Sev	N, M, R, H, S, C	BI	11 (P), 15 (P), 16 (P), 19 (P), 21 (P), 26 (P), 27 (M), 30 (P), 34 (M), 38 (P), 42 (M), 46 (M), 49 (M), 51 (P)
Timber RS	*Crotalus horridus*	NAm	Sev	L, G, S	I	11 (P)
Rock RS	*Crotalus lepidus*	NAm	? Mod	? L	I	11 (P)
Speckled RS	*Crotalus mitchellii*	CAm, NAm	Mild	L, G	I	11 (P)
Black tailed RS	*Crotalus molossus*	NAm, CAm	Mod	? L, G	I	11 (P)
Mexican lance headed RS	*Crotalus polystictus*	CAm	Mod	L, G, H, C	I	11 (P), 17 (P)
Twin spotted RS	*Crotalus pricei*	NAm	? Mod	? L	I	11 (P)
Red diamondback RS	*Crotalus ruber*	NAm, CAm	Mild	L, G	I	11 (P)

Table 32.1 *continued*

Snake	Scientific name	Distribution	Lethality	Venom effects	First aid	Antivenom
Mojave RS	*Crotalus scutulatus*	NAm, CAm	Sev	depends on specimen some L, G, S, C, H etc. some N (usually mild)	I	11 (P)
Tiger RS	*Crotalus tigris*	NAm	Mod	L, S, G	I	11 (P), 13 (P), 15 (P), 16 (P), 17 (P)
Mexican dusky RS	*Crotalus triseriatus*	CAm	Mod	L, G, S	I	11 (P), 17 (P)
Western or prairie RS	*Crotalus viridis*	NAm			I	11 (P), 17 (P)
Ridge nosed RS	*Crotalus willardi*	NAm, CAm	Mild		I	11 (P)
Hundred pace viper	*Deinagkistrodon acutus*	China, Taiwan			I	104 (M), 106 (M), 108 (M)
Hump nosed viper	*Hypnale spp.*	Sri Lanka, India	Mild to Mod	L, S	I	NA
Bushmaster	*Lachesis muta*	CAm, SAm	Sev	L, G, S	I	11 (P), 21 (P), 24 (M), 28 (M), 31 (P), 39 (P), 41 (M), 43 (P), 45 (M)
Mexican horned pitviper	*Ophryacus undulatus*	CAm	? Mod	? L, S	I	? 18 (P)
Hognosed and montane pitvipers	*Porthidium spp.*	CAm	Mild to mod	L, G	I	21 (P), 13 (P), 18 (P)
Godmans montane pitviper	*Porthidium godmani*	CAm	Mild	L, G	I	21 (P)
Rainforest hognosed pitviper	*Porthidium nasutum*	SAm, CAm	Usually mild, occasionally sev	L, G	I	21(P)
Jumping pitviper	*Porthidium nummifer*	CAm	Mild	L, G	I	13 (P), 18 (P), 21 (P)
Slender hognosed pitviper	*Porthidium ophryomegas*	CAm	Mild	L, G	I	21 (P)
Massasauga	*Sistrurus catenatus*					11 (P)
Pigmy rattlesnake	*Sistrurus miliarius*					11 (P)

Tree pit vipers	*Trimeresurus spp.*	East Asia	Mild to Sev	L, S, H, C	I	11 (P), 78 (P), 79 (P), 88 (P)
White lipped tree viper	*Trimeresurus albolabris*	India, China, SEAsia	Mild to Mod	L, S, H	I	? 88 (M), 11 (P)
Okinawa habu	*Trimeresurus flavoviridis*	Amami and Okinawa islands	Mild to Mod	L, S, H, G	I	109 (M), 116 (M)
Indian green tree viper	*Trimeresurus gramineus*	India	Mild to Mod	L, S, H	I	? 88 (M), 11 (P)
Chinese habu	*Trimeresurus mucrosquamatus*	Taiwan sth China, Indochina, Myanmar	Mild to Mod	L, S, H, G	I	101 (P)
Popes pitviper	*Trimeresurus popeorum*	SEAsia	Mild to Mod	L, S, H	I	88 (M)
Shore pitviper	*Trimeresurus purpureomaculatus*	Bengal to SEAsia	Mild to Mod	L, S, H	I	? 88 (M), 11 (P)
Chinese mountain pitviper	*Trimeresurus monticola*	Nepal, China to Malaysia	Mild to Mod	L, S, H	I	? 88 (M), 11 (P)
Chinese green tree viper	*Trimeresurus stejnegeri*	Taiwan, China	Mild to Mod	L, S, H	I	101 (P)
Waglers pitviper	*Trimeresurus wagleri*	SEAsia	Mild to Mod	L, S, H	I	? 88 (M), 11 (P)

Table 32.1 *(end)*

Table 33.2. *List of antivenoms available (based on Ref. [93]).*
Antivenom Numbers listed for each product are only for cross-referencing to Table 32.1 recommendations for antivenom.

Antivenom manufacturer	Phone	Fax [Telex]	Antivenom number	Antivenom name
INSTITUT PASTEUR, Rue du Docteur, Laveran, Algiers, ALGERIA	213-265 3497		1	Antiviperin
INSTITUT PASTEUR, Place Charles Nicolle, Casablanca, MOROCCO	212-227 5778		2	Antiviperin sera
INSTITUT PASTEUR, 13 Place Pasteur, Tunis, TUNISIA	216-1-2830224	[14391 PASTU]	3	Antiviperin sera
AL ALGOUSA SHAREA, Alvezara, Cairo, EGYPT	20-2-257 5829		4 5	Anti Cerastes Polyvalent antivenom
SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH, PO Box 1038, Johannesburg 2000, SOUTH AFRICA	27-11-725 0511	[4-22211]	6 7 8	Polyvalent antivenom Echis antivenom Boomslang antivenom
FITZSIMONS SNAKE PARK, PO Box 1, Snell Parade, Durban, SOUTH AFRICA	27-31-37 6456		9 10	Dendroaspis antivenom Polyvalent antivenom
WYETH AYERST LABORATORIES, PO Box 8299, Philadelphia, PA 19101-1245, USA	1-215-688 4400		11 12	Wyeth antivenin (Crotalidae) polyvalent North American coral snake antivenin
LABORATORIOS MYN S.A., Av. Coyoacan 1707, Mexico 12 D.F., MEXICO			13 14 15 16	Snake antivenin Monovalent Bothrops Polyvalent Crotalus Polyvalent Mexico
GERENCIA GENERAL DE BIOLOGICOS Y REACTIVOS, Secretaria de Salud, Amores 1240, Colonia del Valle, Mexico 03100, D.F., MEXICO	52-575 9155	[1764004 GGBR ME]	17 18	Anti Crotalus Anti Bothrops

Antivenom manufacturer	Phone	Fax [Telex]	Antivenom number	Antivenom name
GRUPO PHARMA, S.A. de C.V., Zapata Labs, Mexico City, MEXICO	52-5-592 8270		19	Suero Antiofidico
INSTITUTO CLODOMIRO PICADO, Universidad de Costa Rica Ciudad Universitaria, Rodrigo Facio, San Jose, COSTA RICA		[UNICORI 2544]	20	Anticoral (polyvalent)
			21	Polyvalent Antivenom
			22	Panamerican Serum (anticoral)
			23	Anticoral (monovalent)
			24	Anti Laquesico
INSTITUTO NACIONAL DE HIGENE Y MEDICINA TROPICAL "Leopoldo Izquieta Perez", Casilla Postal 3961, Guayaquil, EQUADOR			25	Anti Bothrops
INSTITUTO NACIONAL DE SALUD, Av Eldorado con Carrera, Zona G., Bogota D.E., COLUMBIA	57-1-222 0577		26	Antiophidico Polyvalente
INSTITUTO BUTANTAN, Av Vital Brazil, Caixa Postal 65, Sao Paulo SP, BRAZIL	55-11-813 7222	55-11-815 1505	27	Anticrotalic
			28	Antilaquetico
			29	Antibotropico
			30	Antiophidico Polyvalent
			31	Antibotropico laquetico
			32	Antilapidico
INSTITUTO VITAL BRAZIL S.A., Caixa Postal 28, Niteroi, Rio de Janeiro, BRAZIL	55-21-255 8688		33	Soro Antibotropico
			34	Soro Anticrotalico
			35	Soro Antiofidico Polyvalente
FUNDACAO EZEQUIEL DIAS, Rua Conde Pereira Carneiro 80, 30500 Belo Horizonte, BRAZIL	55-31-332 2077	55-31-332 2534	36	Antibotropico
			37	Anticrotalico
			38	Antibotropico Crotalico
			39	Antibotropico Laquetico

INSTITUTOS NACIONALES DE SALUD, Departamento de Animales Venenosos, Calle Capac Yupanquui no 1400, Apartade no 451, Lima, PERU	51-14-416 141		40	Suero Antibotropico Polyvalente
			41	Suero Antilachesico
			42	Suero Anticrotalico
INSTITUTO NACIONAL DE HIGENE, Lima, PERU			43	Bothrops Polyvalent
			44	Anti coral Polyvalent
			45	Suero Antilachesico
			46	Suero Anticrotalico
INSTITUTO NACIONAL DE MICROBIOLOGIA, "Dr. Carlos G. Malbran", Av Velez Sarsfield 563, Buenos Aires, ARGENTINA			47	Antibothrops Bivalente
			48	Antibothrops Tetravalente
			49	Anticrotalus
			50	Antimicrurus
			51	Tropical Trivalente
EJERCITO ARGENTINO, Campo de Mayo, Batallon 601, Pcia de Buenos Aires, ARGENTINA			52	Antibothrops Bivalente
			53	Antimicrurus
UNIVERSIDAD CENTRAL DE VENEZUELA, Caracas, VENEZUELA	58-2-719 450		54	Suero Antiofidico Polyvalente UCV
MINISTRY OF HEALTH, Department of Laboratories, PO Box 6115, Jerusalem, ISRAEL	972-2-381 631	972-2-781 456	55	Anti-Echis Coloratus
			56	Anti-Vipera Palestinae
ROGOFF MEDICAL RESEARCH INSTITUTE, Tel Aviv, ISRAEL			57	Arabian Echis
DEPT. OF ZOOLOGY, Tel Aviv University, Tel Aviv, ISRAEL	972-3-545 9820		58	Anti-Walterinnesia
			59	Palestine Viper
INSTITUT D'ETAT DES SERUMS ET VACCINS, Razi Hessarek, BP 656, Teheran, IRAN	98-2221 2005		60	Polyvalent Antivenom
			61	Naja Antivenom
			62	Echis Antivenom
			63	Lebatina Antivenom
			64	Persica Antivenom
			65	Latifi Antivenom
			66	Agkistrodon Antivenom

***Table 33.2**. List of antivenoms available (continued)*

Antivenom manufacturer	Phone	Fax [Telex]	Antivenom number	Antivenom name
CENTRAL RESEARCH INSTITUTE, (Simla Hills), (HP) Kasauli, INDIA			67	Polyvalent Snake Venom Antiserum
			68	Bivalent Antiserum
			69	Monovalent Cobra Venom Antiserum
			70	Monovalent Krait Venom Antiserum
			71	Monovalent Russells Viper Venom Antiserum
			72	Monovalent Echis Venom
HAFFKINE BIOPHARMACEUTICAL CO. Ltd., Acharya Donde Marg, Parel, Bombay 400012, INDIA	91-22-412 9320-23	[11-71427 HBPC IN]	73	Polyvalent Antisnake Venom Serum
			74	Bungarus
			75	Naja
			76	Vipera
			77	Echis
SERUM INSTITUTE OF INDIA Ltd., 212/2 Hadapsar, Pune 411 028, INDIA	91-212-672016	91-212-672040	78	Sii Polyvalent Antisnake Venom Serum Lyophilized
			79	Sii Bivalent Antisnake Venom Serum
NATIONAL INSTITUTE OF HEALTH, Biological Production Division, Islamabad, PAKISTAN	92-51-20797	[5811-NAIB-PK]	80	Polyvalent Antisnake Venom Serum
			81	Monovalent Naja Naja
			82	Monovalent Krait
			83	Monovalent Russells Viper
			84	Monovalent Echis
INDUSTRIE AND PHARMACEUTICAL CORPORATION, Yangon, MYANMAR			85	Bivalent
			86	Siamese Cobra
			87	Russells Viper

THAI RED CROSS SOCIETY, Queen Saovabha Memorial Institute, Bangkok, THAILAND	66-2-252 7789		88 89 90 91 92 93	Green Pit Viper Antivenin Cobra Antivenin King Cobra Antivenin Banded Krait Antivenin Russells Viper Antivenin Malayan Pit Viper Antivenin
THAI GOVERNMENT PHARMACEUTICAL ORGANIZATION, Bangkok, THAILAND	66-2-246 0042		94	Anti Malayan Pit Viper Venom Serum
PERUM BIO FARMA (Pasteur Institut), Jl. Pasteur 28, PO Box 47, Bandung, INDONESIA	62-22-83755-56-57	[38432 biofar ia]	95 96 97 98	Polyvalent Antivenom Serum Malayan Pit Viper Banded Krait Malayan Cobra
SERUM AND VACCINE LABORATORIES, Alabang Multinlupa, Rizal, PHILIPPINES			99	Cobra
NATIONAL INSTITUTE OF PREVENTATIVE MEDICINE, 161 Kun Yang Street, Taipei, TAIWAN	886-2-371 6831		100 101 102 103 104	Naja-Bungarus Antivenin Trimeresurus Antivenin Naja Bungarus Agkistrodon
SHANGHAI VACCINE AND SERUM INSTITUTE, 1262 Yang An Road, Shanghai, CHINA			105 106	Mamushi Monovalent
MINISTRY OF PUBLIC HEALTH, Shanghai Institute of Biological Products, Shanghai, China	86-21-513 189	[3036951 BP CN]	107 108	Antivenom of B. multicinctus Monovalent
THE CHEMO-SERO-THERAPEUTIC RESEARCH INSTITUTE, 668 Okubo, Shimizo, Kumamoto 860, JAPAN			109 110	Habu Antivenom Mamushi Antivenom
TAKEDA CHEMICAL INDUSTRIES Ltd., Osaka, JAPAN	81-6-204 2111	81-6-204 2880	111	Mamushi Antivenom

***Table 33.2**. List of antivenoms available (continued)*

Antivenom manufacturer	Phone	Fax [Telex]	Antivenom number	Antivenom name
JAPAN SNAKE INSTITUTE, Yauzuka-honmachi, Nitta-gun, Gunma Prefecture 379-23, JAPAN			112	Anti-Yamakagashi
RESEARCH FOUNDATION FOR MICROBIAL DISEASES, Osaka University, Osaka, JAPAN	81-6-877 5121	81-6-876 1984	113	Dried Mamushi Antivenom
KITASATO INSTITUTE, Minato-ku, Tokyo, JAPAN	81-3-444 6161		114	Mamushi Antivenom
CHIBA SERUM INSTITUTE, 2-6-1 Konodai, Ichikawa, Chiba, JAPAN			115	Dried Mamushi Antitoxin
			116	Adsorbed Habu Toxoid
PASTEUR MERIEUX SERUM ET VACCINS, 1541 Av Marcel Merieux, 69280 Marcy l"Etoile, Lyon, FRANCE	33-7887 3232	33-7887 3854	117	IPSER Europe
			118	Bitis Echis Naja
			119	IPSER Afrique
			120	Near and Middle East
			121	Cobra
			122	Dendroaspis
			123	IPSER V
			124	Serum Antivenimeux Purifie Merieux
			125	Serum Antivenimeux Lelong
BEHRINGWERKE AG, Postfach 11 40, 3550 Marburg/Lahn 1, GERMANY	49-6421-39-0	49-6421-313 88	126	Europe
			127	North Africa
			128	Central Africa
			129	Near and Middle East
TWYFORD PHARMACEUTICALS GmbH, Postfach 21 08 05, D-6700 Ludwigshafen am Rhein, GERMANY	49-621-589 2688	49-621-589 2896	130	Malayan Pit Viper Antivenom
			131	Cobra Antivenom
INSTITUTO SEROTERAPICO VACCINOGENO, Toscano "Sclavo", Via Fiorentina 1, 53100 Sienna, ITALY			132	Serum Antiviperin

INSTITUTO SEROTERAPICO, Via Darwin 20, Milan, ITALY	39-2-835 6163		133	Vipera Ammodytes
INSTITUTE OF IMMUNOLOGY, Rockerfellerova 2, Zagreb, CROATIA	38-41-430 333	38-41-277 278	134	Antiviperinum
INSTITUTE OF EPIDEMIOLOGY AND MICROBIOLOGY, Sofia, BULGARIA	359-2-701 081		135	Monovalent
INSTITUT SEROTHERAPIQUE ET VACCINAL SUISSE, Case Postale 2707, 3001, Berne, SWITZERLAND	41-31-344 111	41-31-342 808	136	Serum Antivenimeux Berna
CHEMAPOL FOREIGN TRADE Co. Ltd., Kodanska 46, 100 10 Prague 10, CZECHOSLOVAKIA			137	Anti Vipera Ammodytes
SEVAC, Institute for Sera and Vaccines, Prague, CZECHOSLOVAKIA	42-2-250 161		138	Venise
			139	Venise
MINISTRY OF PUBLIC HEALTH, 101 431, GSP 4, Moscow K-51, RUSSIA			140	Polyvalent Serum
			141	Anti Vipera Lebitina
			142	Anti Naja Naja Oxiana
RESEARCH INSTITUTE OF VACCINE AND SERUM, Ministry of Public Health, Tashkent, UZBEKISTAN			143	Monovalent Echis Carinatus
			144	Monovalent Naja Naja
			145	Monovalent Vipera Lebetina
			146	Polyvalent Echis and Naja
			147	Polyvalent Vipera and Naja
CENTRO DE ESTANDARDARIZACION DE VENENOS Y ANTIVENENOS, Apartado de Correos 1486, 08080 Barcelona, SPAIN	34-3-714 0444		148	Polyvalent Antivenom Against Europe, North Africa, Near East Vipers
			149	Polyvalent Antivenom Against Iberian Peninsula Vipers
			150	Specific Serum Against Vipera Latasti

Table 33.2. *List of antivenoms available (continued)*

Antivenom manufacturer	Phone	Fax [Telex]	Antivenom number	Antivenom name
COMMONWEALTH SERUM LABORATORIES, 45 Poplar Rd., Parkville, Victoria 3052, AUSTRALIA	61-3-389 1911	61-3-389 1434	151	Death Adder
			152	Sea Snake
			153	Taipan
			154	Eastern Brown Snake
			155	Black Snake
			156	Polyvalent
			157	Tiger Snake
			158	Brown Snake

Table 32.2. *List of antivenoms available (end).*

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P. Gopalakrishnakone

33. Dangerous animals (excluding snakes)

BEES, WASPS AND HORNETS

Bees, wasps and hornets are insects of considerable medical importance and can cause health problems to humans especially to children [1]. Hornets are large wasps. They all belong to the insect order *Hymenoptera* (insects with membranous wings); the female has a sting at the terminal end of the abdomen and can inflict a painful and sometimes fatal sting. Therefore, insect stings must be viewed with grave concern. A medical emergency can occur with a single sting, especially for those who are hypersensitive to hymenopteran venom [2]. It can cause anaphylactic shock.

Ways of encounter

Wasps and bees pose a threat to man because of man's occasional encounter either accidentally or intentionally. Wasps and bees occasionally build their nests near to human dwellings, for example in roof spaces, trees, bushes and shrubs around houses. Wasps and bees while foraging for food are often attracted by light inside dwellings, bringing them into contact with man. Nests of wasps and bees are sometimes accidentally disturbed or destroyed by man, for instance by horticulturists attending to plants and fruit trees. Hymenopteran nests can also be intentionally destroyed or disturbed, for instance by children throwing stones at them. Once their nests are disturbed, wasps and bees will go into a frenzy and attack any moving object, normally man and animals in the vicinity.

Stings

The bee sting is barbed at the end like a fish hook, thus it is always left behind in the wound resulting in the subsequent death of the bee. Therefore, bees can only sting once. Wasps, on the other hand, have unbarbed stings. Therefore, they are able to sting their victims repeatedly without having to lose their stings and die. The bee sting always includes the sting and venom gland

in the wound unless brushed off, while the hornet sting leaves only a puncture mark, which is usually larger than that made by the bee sting. The sting is a modified ovipositor (egg-laying tube) and is therefore only found in the female. The male wasps and bees do not possess stings but have mandibles that can bite. The sting is used for offence and defence. The stinging apparatus comprises several interconnected sclerotised (hard) external parts including the sting and several interconnected unsclerotised (soft) internal parts containing the poisons sac, the acid glands, and the alkaline gland. The external sclerotised parts are structured for stinging through muscular action while the unsclerotised structures secrete the venom.

Clinical reactions

Sting reaction from bees and wasps can be categorised into local and general reactions.

Local reactions usually take the form of pain and swelling at the site of the sting. The intensity of swelling around the wound depends very much on the part of the body stung. Normally the swelling resolves within 24 hours.

General reactions. In the moderate form, there may be widespread swelling and rash accompanied by itchiness. In the severe form, the patient may go into shock and collapse. It may occur immediately after the sting or may take as long as 12 hours to appear. Generally, the greater the number of stings, the more severe the reaction. Thus, medical attention must be sought immediately to protect the victim's life.

Treatment

The barbed stings of the bees should be removed from the site of sting by scraping the skin with the blade of a knife or with fine tweezers without squeezing the venom gland. The wound can be dressed with local antiseptics if necessary. If there is anaphylactic reaction [2], then adrenaline should be given by injection. The dose is 0.1% (1:1000) adrenaline (0.5–1 ml in adults or 0.01 ml/kg in children) by subcutaneous injection. Severe envenomation by multiple stings should be treated with adrenaline and antihistamines, and symptomatic measures. Patients may develop acute renal failure.

SCORPIONS

Scorpion bites are a not infrequent medical problem in many parts of the world [3–6]. Scorpions have 4 pairs of legs, a pair of claws and a segmented tail. The terminal segment of the tail, known as a telson, contains venom glands, connected to the needle-sharp tinger with 2 small orifices through which the venom is ejected. Most scorpions are nocturnal and feed on other insects. In the day, they hide under logs and rocks, or cavities and crevices.

Species	Geographic distribution
North America:	
Centruroides exilicauda	South-West U.S., North Mexico
C. l. limpidus	Mexico
C. noxius	Mexico
C. s. suffusus	Mexico
Tityus trinitatis	West Indies
South America:	
T. bahiensis	Argentina, Brazil
T. cambridgei	Guyana
T. serrulatus	Brazil
T. trinitatis	Venezuela
Africa and Middle East:	
Androctonus australis	Algeria, Egypt, Morocco
A. crassicauda	Israel, Iraq, Turkey
Buthus occitanus	Morocco, Algeria, Jordan
Hottentotta minax	Sudan
Leiurus quinquestriatus	Egypt, Israel, Turkey
Parabuthus sp.	South Africa
India:	
Mesobuthus tamulus	South India

***Table 33.1**. Geographic distribution of some medically important scorpions*

The order *Scorpiones* has nine families and about 1400 species and subspecies have been described [7], of which only some are of medical importance and cause fatalities in humans. They usually belong to the family Buthidae: the genera includes *Androctonus*, *Buthacus*, *Buthus*, *Centruroides*, *Leiurus*, *Mesobuthus*, *Parabuthus*, and *Tityus*. A list of the species and their geographical distribution is shown in Table 33.1 [8]. A more extensive listing was given by Keegan [9].

Clinical features

Local reactions include severe pain and mild oedema.

General reactions. Scorpion envenomation may result in parasympathomimetic symptoms, characteristically described as "autonomic storm", with increased blood pressure, bradycardia, mydriasis and increased salivation, cardiac manifestations [10,11] with decreased blood pressure, myocardial damage resulting in pulmonary oedema or evidence by asymptomatic ECG changes, and central nervous system manifestations. Envenomations are usually more severe in children [6].

Antidote	Source	Venoms	Specific name
Scorpion antivenom	Institut Pasteur, Algiers, Algeria	North African sc.	*Androctonus*, *Australis hector*
Scorpion antivenom	Institut Pasteur, Casablanca, Morocco	North African sc.	*A. mauretanicus*
Antiscorpionic serum	Institut Pasteur, Tunis, Tunesia	North African sc.	*A. australis*, *B. occitanus*
Scorpion antivenom	South African Institute for Medical Research Johannesburg	South African sc. (North Transvaal)	*Parabuthus*, *Transvaalicus*
Antivenin *Centruroides*	Laboratorios MYN Mexico City	Central America sc.	*Centruroides* spp.
Antialacras polyvalent	Laboratorios Zapata, Mexico City	Scorpion	*C. suffusus*, *C. noxius*
Alacramyn, lyophilized antiscorpion serum	Laboratorios Zapata, Mexico City	Scorpion	*C. noxius*, *C.s. suffusus*, *C.l. limpidus*
Soro antiscorpionico genys *Tityus*	Instituto Butantan Sao Paulo, Brazil	Brazilian scorpion	*Tityus serrulatus*, *T. bahiensis*
Antivenin	Reyfik Saydam Central Institute of Hygiene Ankara, Turkey	Israeli scorpion, Yellow scorpion	*A. crassicauda*, *Leiurus quinquestriatus*
Scorpion antivenom Twyford	Twyford, Ludwigshafen am Rhein, Germany	North African scorp.	*A. australis*, *B. occitanus*, *L. quinquestriatus*
Polyvalent scorpion antivenom	Institut d'Etat des Sérums et Vaccins, Teheran	Israeli scorpion, Scorpions	*Androctonus crassicauda*, *Buthotus salcyi*, *Mesobuthus eupeus*, *Odontobutus doriae*, *Scorpio maurus*
Monovalent scorpion venom antiserum	Central Research Institute, Kasauli, India	Indian red scorpion	*Buthus tamulus*
Scorpion antivenom	Lister Institute, Elstree, Herts., UK	North African sc., Yellow scorpion, Israeli scorpion	*A. australis*, *B. occitanus*, *L. quinquestriatus*, *A.crassicauda*

Table 33.2. *Commercially available scorpion antivenoms (adapted from Ref. [15])*

Treatment

Treatment methods are controversial [12,13]. Symptomatic treatment of autonomic storm with vasodilators or a combination of nifedipine and prazosin has been shown to be effective [14]. Antisera are available as indicated in Table 33.2 [15]. However, it remains to be established which envenomations and which patients are more likely to benefit from antivenom therapy [6]. A recent study in 151 envenomations showed that *Centruroides sculpturatus* antivenom appears to be safe (with 8% of mild hypersensitivity reactions) and effective [16].

SPIDERS

Poisons Centers receive many enquiries about spider bites. Only a few patients suffer serious envenomation so that the majority develop local reactions only [17–19]. Spider envenomation may be reported in many countries as illustrated by a recent series of 30 cases from France's Marseilles Poisons Centre [20].

All species are considered venomous, as most of them possess a pair of venom glands [3]. The venom glands of primitive spiders, such as tarantulas are quite small and situated inside the jaws. In contrast, most other spiders have relatively large poison glands that may extend out of the jaws and reach far into the forebody. Each poison gland consists of a long cylindrical sac and an adjoining duct which opens slightly away from the tip of the fang. There are about 30,000 species of spiders in the world, only 20–30 are potentially dangerous to man. The most important spiders in relation to human health are shown in Table 33.3. The principal venomous spiders of Brazil have been recently described [22].

Clinical features

There will be pain at the site of bite, followed by swelling and redness.

Neurotoxic symptoms are mainly seen after bites by *Latrodectus* and include headache, nausea, vomiting muscle spasms and tremors. Cardiovascular symptoms might also be present.

Necrotic symptoms are seen mostly after *Loxoscelis* bites [20]. Following the painful bite, the skin turns dark and black and then became an eschar with dry skin [23]. The lesions sloughs in few days and a deep, granular area surrounded by normal skin will appear. This ulcer may take many weeks for healing. Systemic reaction such as intravascular hemolysis and hemoglobinuria also can occur as recently described in a 12-year-old female following bite by a brown recluse spider (*Loxosceles reclusa*) ([24].

There may be mixture of neurotoxic as well as necrotic type of reactions as observed following bites by spiders belonging to *clubionidae*, *chiracanthium*.

Mygalomorphae (Tarantulas, bird spiders, trap door spiders)

1. Family *Ctenizidae* (Trap door spider): Europe and Mediterranean region
2. Family *Dipluridae* (Funnel-web spider) e.g. *Atrax robustis* (Sydney-funnel web spider), *A. formudabilis*: Australia, South America
3. Family *Theraphosidae* — Hairy tarantulas: universal
4. Family *Bonychelidae* — Baboon spider: Australia, South Africa

Arachnomorphae (True spiders)

1. Family *segestridae*
2. Family *scytodidae* e.g. *Loxosceles sp.* (Brown recluse spiders): South America and some parts of U.S.A. and Canada
3. Family *Theridiidae* e.g. *Latrodectus sp.* (widow spiders)
4. Family *Agelenidae*
5. Family *Lycosidae*
6. Family *Clubionidae*
7. Family *Ctenidae* e.g. *Pheneutria sp* (Banana spider)

Table 33.3. *Medically important venomous spiders of the world (adapted from Ref. [21])*

Treatment

Treatment of spider bites has been recently reviewed, with special reference to Australian spiders [26]. A crepe bandage could be used to splint the bitten limb and specific antivenom (see Table 33.4) should be administered. Oral dapsone (100 mg b.d.) could be given to necrotic types. Calcium gluconate (10 ml of 10% solution iv) is used in *Latrodectus* bites to reduce the muscle spasm.

Centipedes

These are usually found in soil, litter or under stones or barks. The body is soft and flattened and have from 20 to 100 pairs of legs, one pair to each trunk segment. They are brightly coloured, reddish brown, black or green. The legs of the first trunk segment form the poison-claw in which the venom gland lies. This is used to seize the prey. They can inflict painful bites and at the site of bite, itching erythema, inflammation and blistering can occur. Local necrosis can occur but rare. The treatment is usually confined to the treatment of the wound with dressing and antibiotics if necessary. No antivenom is available.

VENOMOUS FISHES

Some marine fishes are venomous [26,27]. These fishes are armed with spines which possess venom, produced by specialised glandular cells. The venom is

Antidote	Source	Specific name	Spider
Spider antivenom	South African Institute for Medical Research Johannesburg	Black widow spider	*Latrodectus mactans (indistinctus)*
Antivenin	Merck Sharp & Dohme, Rahway NJ, USA	Black widow spider	*Latrodectus mactans*
Soro antiarchnidido polyvalente	Instituto Butantan, Sao Paulo, Brazil	Banana spider, Brown recluse spider	*Phoneutria* spp., *Loxosceles* spp.
Soro antiloxoscelico	as above	Brown recluse spider	*L. reclusa*
Suero antiloxoscelico	Institutos Nacionales de Salud, Lima, Peru	Brown recluse spider	*Loxosceles* spp.
Antiladrodectus mactans serum	Institute Immunology, Zagreb, Croatia	European widow	*L. mactants t treredecimguttatus*
Red-backed spider antivenom	Commonwealth Serum Laboratories, Parkville VA, Australia	Red-backed spider	*L. hasselti hasselti*
Funnel-web spider antivenom	as above	Sydney funnel-web spider	*Atrax robustus*

Table 33.4. *Commercially available spider antivenoms (adapted from Ref. [15])*

injected through the spine of the fish into the wound causing intensive pain and sometimes death. Thus, these fishes should be handled with caution. Common venomous fishes are catfishes, rays, scorpion-fishes and rabbit-fishes [28].

Description

Catfishes are easily recognised by their elongated and scaleless bodies and the presence of tentacles or barbels around the mouth. Most of these fishes have the dorsal and pectoral fins armed with strong, curved and often serrated spines which contain venomous glands. These fishes can be found in rivers and shallow seas, in the mud near shores and river mouths, and some in coral reefs.

Rays are commonly found in the seas and lower reaches of rivers. They bury themselves in the sea-bed and use their spines for defence. A sting can occur when the ray is stepped on accidentally. The rays are divided into 3 categories:

- Sting ray (family *Dasyatididae*)
- Eagle ray (family *Myliobatididae*)
- Long-tailed butterfly ray (family *Dasyatididae*)

The scorpion-fishes can be divided into 3 broad categories:

- The zebra-fish or lion-fish (family *Scorpaenidae*) which can be easily recognised by their elongated fins and striking coloration.

- The scorpion-fish proper is also of the same family as the zebra-fish or lion-fish.
- The stonefish (family *Synanceiidae*), which usually lies quietly on rocky bottoms and is extremely well camouflaged.

Rabbit fishes (family *Siganidae*) swim about in schools and feed on seaweeds. The venom glands lie within the spines of the dorsal, pelvic and anal fins.

Clinical features

Local reactions are characterized by sudden intense pain at the site of sting which increases in intensity and gradually spreads to the adjacent area (e.g. from toe to leg and thigh). The pain may last for few hours to days, and may be followed by tenderness for several days. The puncture wound is prone to secondary infection.

General reactions include fainting attacks, pale clammy skin, increased heart rate and signs of shock. Regional lymph nodes (e.g. in groin or axilla) become swollen and tender. Nausea and vomiting may be present. Fatalities are rare.

Management

Stonefish. Pain is very severe at the site of sting. The first-aid treatment is much the same as that of sting ray except that the venom in stonefish is much more potent. A special antivenom for stonefish venom is available from Commonwealth Serum Laboratories, Australia.

Sting ray. Pain at the site of sting is immediate. If no pain killer drug is available, a venous tourniquet should be applied above the site as soon as possible. Immerse affected part in warm water, if available, without scalding the skin. Wash the wound with clean water and prevent infection by covering with a clean dressing. Immobilise the limb that is affected and raise it to prevent too rapid return of the toxin to the heart. If the spine is present at the site of the wound, it should be gently removed.

Should the patient stop breathing, CPR is indicated and should be continued until taken over by proper medical aid. Lie the patient down and do not move him. Elevate the affected area (e.g. leg). Remove any broken spines, clean the wound, encourage bleeding. Dipping in warm water the affected part (without scalding) will do a lot to relieve the pain. Application of a weak solution of potassium permanganate (Condy's crystals) may have some effect in relieving the pain.

FISH POISONING

Poisonous fishes are those which cause poisoning when eaten, in contrast to the venomous fishes like stone fishes which possess venomous spines with which they inflict nasty stings. There are three types of fish poisoning that are common, namely tetrodotoxic, ciguatera and scombroid poisoning [29].

Antitrachinus scorpaena uranoscopus	Institute of Immunology, Zagreb, Croatia	Weever fish, Scorpion fish, European star	*Trachinus* spp., *Scorpaena* spp., *Uranoscorpus* spp.
Scorpion fish antivenom	as above		*Scorpaena porcus*
Weever fish antivenom	as above	Weever fish	*Trachinus* spp.
Stonefish antivenom	Commonwealth Serum Lab., Parkville, Australia	Stonefish	*Synanceja trachynis* or *S. vrrucosa*

Table 33.5. *Commercially available fish antivenoms (adapted from Ref. [15])*

Pufferfish poisoning

Tetrodotoxic poisoning occurs following the ingestion of pufferfish, boxfish or porcupine fish. This is also known as puffer or fugu poisoning. The poisoning is due to toxin known as tetrodotoxin which is concentrated in the internal organs such as liver, ovary and intestines. The skin also contains some glands which secrete these toxins. Usually the body muscles are free of the toxin.

Puffers are fishes which have the ability to inflate themselves to an enormous size. They belonged to two families: *Diodontidae* (porcupine fishes) and the *Tetradontidae* (puffers). They are popularly called puffers. Together with the spike fishes (*Triacanthodidae*), the triplespines (*Triacanthidae*), the triggerfishes and the fishes (*Balistidae*), the boxfishes (*Ostraciontidae*), and the molas (*Molidae*), they belong to the order *Tetraondotiforme*.

Tetrodotoxin is the most lethal of the fish poisons. The toxin is an amino perhydroquinazoline, slightly soluble in water with a molecular weight of 319. The toxin interferes with neuromuscular transmission in motor and sensory nerves and the sympathetic nervous system. Its effect is on sodium transport. It has depressant effect on skeletal and cardiac muscles. It has anticholinesterase activity. Heat does not inactivate the toxin.

Symptoms depend on the amount of poison in the ingested fish flesh and also in the individual. Usually within 10 to 45 minutes the symptoms appear, but rarely there might be a delayed reaction ranging from 3–24 hours. Numbness around the mouth, a tingling sensation in the tongue and mouth are early features followed by nausea and sometimes vomiting. Headache, increased salivation and diarrhoea also might be present. Later, there is difficulty in swallowing, difficulty in breathing, muscle paralysis, inability to talk or walk which might be followed by death. Hypertension is an usual feature of tetrodotoxin poisoning [29].

Specific advice is to avoid eating scaleless fish. If someone is interested in tasting Fugu in Japan, do so at a first-class Japanese restaurant with a licensed puffer cook. Cooking by any means (e.g. frying, boiling, baking) will not inactivate the toxin.

Ciguatera poisoning

Ciguatera poisoning is due to the consumption of fishes contaminated with ciguatoxin, a toxin which acts as a sodium channel agonist [30,31]. This toxin is produced by a microscopic marine dinoflagellate *Gambierdiscus toxicus* and through the food chain it reaches the fish, mainly the reef fishes. The toxin accumulates mainly in the liver and testis of the fish as well as other viscera, while the flesh (muscle) of the fish is much less affected. Cooking or storage of the fish has no effect on the toxicity. Some of the fishes which have been implicated with ciguatera poisoning are groupers, barracuda, amberjack, sturgeon fish.

Ciguatera is common in many tropical areas and although mortality is low, symptoms are often prolonged and debilitating [32]. Symptoms appear within minutes of consuming the contaminated fish. The features are similar to any food poisoning, such as nausea, vomiting, headache and diarrhoea but the characteristic features are the neurological symptoms which include a tingling sensation, numbness of the tongue, mouth, throat and lips. Painful tingling of the palms of hands and soles of feet on contact with cold water can occur. Muscle pain and weakness, reduced reflexes, difficulty in walking and joint pain are other effects. The general features also include recurrent burning sensation in many parts of the body associated with rashes. Coma is rarely seen but has been reported [33]. Bradycardia and hypotension may occur [34,35].

Specific advice is to be careful when buying oversized fish. If someone is suspicious of a potentially poisonous fish, but there is no other choice (e.g. ship wrecked at sea), the roe, intestines and viscera should then be avoided.

Scromboid poisoning

Scromboid poisoning is a form of food poisoning caused by eating spoiled fish that have undergone toxic changes due to the action of bacteria on the spoilt fish tissue. Most cases of poisoning are attributed to the eating of mackerel, mackerel-like fishes, the tunas, etc. These are fish which are normally safe to eat, but can become poisonous if prepared wrongly or stored incorrectly. If the fish is stored at room temperature or above 20°C for several hours or in the sun they are predisposed to bacterial action. The bacteria involved include *Proteus morganii* and *P. vulgaris* and also *Clostridium, Escherichia, Salmonella* and *Shigella* have been implicated. These bacteria act on the flesh of the fish and cause an increase in histamine levels in the tissue so that histamine is considered as the major cause of clinical toxic symptoms [36].

Symptoms are similar to histamine poisoning. They usually appear 0.5–1 hour after eating the fish. It will have an unusual taste (sharp, hot, metallic or irritating). Nausea, vomiting, diarrhoea, abdominal discomfort or pain, headache, burning sensation in the throat, dry mouth and difficulty in swallowing are early symptoms which may be followed by a generalized red colour rash over the whole body, respiratory difficulty and muscle weakness.

Specific advice is to prepare the fish correctly and store it if necessary by refrigeration. Fish should not be stored at room temperature for a long time. When buying fish in the market, if there is any evidence of pallor of the gills (usually it should be bloody red) or odour, the fish should be discarded. Avoidance is the best policy. There is no easy way of distinguishing safe from poisonous fish. The safest way maybe is to rely on local knowledge. But the fact remains, however, that it is far better not to eat suspected flesh than to take a chance.

Clinical features after ingestion of poisonous fish

Symptoms and signs vary depending upon the person and the amount of poisonous fish ingested. Symptoms appear from as short as 10 minutes to as long as 3 hours after ingestion.

Numbness around the mouth, tiredness, giddiness, sweating, salivation, headache, nausea, vomiting, diarrhoea and abdominal pains are early features. Delayed features include difficulty in breathing, cyanosis, muscle twitching, tremors and extensive muscular paralysis, leading on to unconsciousness and death.

The treatment is essentially supportive. Induced emesis is used if the patient is conscious and has neither difficulty in swallowing nor weakness of voice. Vomitus which may contain fish remnants should be collected for specific laboratory investigations. No specific treatment or antidotes are available.

DANGEROUS ECHINODERMS AND MOLLUSCS

The poisonous and venomous marine species belong to the phyla *Echinodermata* consists of sea urchins, starfishes, brittlestars, crinoids and sea cucumbers while well-known groups within the phylum *Mollusca* are the gastropods, bivalves and cephalopods [37]. Both phyla contain venomous as well as poisonous species. Venomous species inject their toxin into the victim through spines or other similar structures while poisonous species contain poison within their tissues which affect the victim. Venomous species can be eaten after being cooked but poisonous species should never be eaten as the poison will not be inactivated by high temperature.

Phylum echinodermata

There have been scattered reports of poisoning by starfishes and sea cucumbers which in most cases is attributed to the presence of saponins in these two groups. Foaming occurs readily on the water surface of aquarium tanks containing these animals because of the saponins. Sea cucumbers when handled, will discharge long sticky threads before eviscerating their gut system. These long threads are apparently harmless although some early reports claim that they cause painful inflammation when in contact with the human skin.

When eaten raw, the saponins cause nausea, but dried sea cucumbers which are commonly eaten, contain a very low level of saponin in their tissues as a result of the treatment process and are safe for human consumption.

The venomous forms of echinoderms are confined to the sea urchins and Crown-of-thorns starfish.

Sea urchin

Removing the spine will be difficult. For first aid, methylated spirit and hot water may help to relieve the pain. Immobilise and raise the limb. Seek medical aid. If spines are small, hitting the area with a firm object may break up the spine into smaller pieces and help in rapid absorption.

Local anesthesia will relieve pain. If the spine can be located by X-ray, surgical removal may be possible followed by wound dressing. Broad spectrum antibiotics should be given to prevent secondary infection. If spines are not removed, nodular or diffuse granulomatous lesions may occur. Local or systemic steroid may be of benefit.

Blue ring octopus

The wound should be washed with clean water. Immobilise and raise the limb. Apply a venous tourniquet above the wound. Release the tourniquet pressure for 1 minute after every 10 minutes. In hospital, endotracheal intubation with artificial respiration may be required. Local anaesthetic should be given to stop pain if necessary. Steroids or antihistamines may be required if there are delayed allergic reactions.

Cone shells

Immobilize and raise the limb. Apply a venous tourniquet above the wound. Release tourniquet pressure for 1 minute after every 10 minutes. Evacuate immediately to the nearest hospital. In hospital, endotracheal intubation with artificial respiration may be required. Respiratory stimulant and drugs against neuromuscular blockage may be indicated. Local anaesthetic should be applied to the wound if the patient complains of pain.

DANGEROUS MARINE COELENTERATES

This section presents some of the venomous marine species of the Phyla *Coelenterata* and *Annelida*. The diversity of these groups together with the lack of detailed studies make it impossible to include all the species, some of which still remain to be positively identified [37]. Nevertheless, the commoner species most likely to be encountered are highlighted.

Phylum coelenterata

Venomous coelenterates can be found within the classes: *Hydrozoa* (hydroids, fire corals and hydromedusae), *Scyphozoa* (true jellyfishes) and *Anthozoa* (sea anemones).

The *Hydrozoa* includes the plant-like hydroids, the fire corals which secrete a calcareous skeleton like stony corals do, and the hydromedusae which are the swimming stages of some species of hydroids and resemble jellyfishes of the class *Scyphozoa*. Not all species of these three classes are venomous and some are relatively harmless. Sea anemones have a wide range of sizes from small to large, and bear tentacles ranging in number from eight to a few hundred encircling a central mouth. Those that feed on active prey such as fish have very potent nematocysts which are painful to man but not fatal.

The most severe envenomations have been attributed to *Physalia physalis*. A serious envenomation was reported in a scuba diver after multiple sting by an Atlantic *Physalia* jellyfish [38]. He developed acute respiratory distress with muscle pain and spasms, and impaired consciousness. Supportive measures were quickly effective but full recovery was delayed for several weeks. However, sudden death has been reported in a 5-year-old child 40 minutes after accidental envenomation with tentacles of the jellyfish *Chiropsalmus quadrumanus* [39].

Symptoms of coelenterate stings can vary from a mild itch to a stinging burning or throbbing pain. The pain may be localised or accompanied by abdominal or chest pain. Fever, vomiting, breathing difficulty, delirium shock and heart failure may follow. The part of the body where the coelenterate had contact may be inflamed with the formation of weals. The more toxic coelenterates may cause blisters and ulcers on the skin. The lymph nodes relating to that part of the body may be swollen and tender.

Management. If tentacles are still on the affected area, remove them gently with wet sand or a glove. Local anesthetic ointment can be applied over the affected area of skin to relieve pain. Morphine may be used if there is severe pain. Local steroid ointment will help to reduce inflammation and itch. Specific antivenom is available from Australia for Box jellyfish sting.

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Human Toxicology, J. Descotes (Ed.)

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34. Environmental hazards

INTRODUCTION

An emerging new field of human toxicology is related to environmental medicine. The public is increasingly concerned about potential environmental hazards to health, especially with the reporting of chemical accidents or catastrophes, such as the events at the Love Canal in the state of New York, the city of Seveso in Italy, or Bhopal in India, and the media has undoubtedly played a role in this growing awareness [1]. Books, such as that by Upton and Graber [2], have been published with the aim of providing the general population with advice for avoiding or limiting these potential health hazards in their daily life. Moreover, the scientific community has paid more and more attention to environment-associated health problems, as exemplified by two very recent textbooks devoted to environmental medicine [3,4].

Environmental medicine was originally proposed as the study of effects upon human beings of external physical, chemical, and biological factors in the general environment [5], but environmental physicians focus more and more on the diagnosis and management of adverse health effects related to the physical and chemical contamination of air, soil or water (i.e. toxic causes in a general sense), and less and less on the area of infectious diseases as in the first half of this century. Others, the clinical ecologists, consider environmental medicine from the viewpoint of patients who are unusually sensitive to very low levels of chemical exposure [6]. Whatever the definition used, one major difference between environmental medicine and ecology, or ecotoxicology, is that the emphasis is on human health rather than environmental quality, although the importance of environmental impacts on human health is fully acknowledged. Therefore toxicologists, because of their increasing involvement in the management of patients with chronic (and not only acute) chemical poisonings, are invited and are increasingly likely to play a critical role in the development of environmental medicine.

This Chapter is obviously not an attempt to cover the whole field of environmental hazards, but instead it overviews some recent issues of major concern, in the hope they can serve as illustrations of this emerging field.

AIR POLLUTION: MORBIDITY AND MORTALITY

As dramatically illustrated by the London fog of 1952 and other episodes, air pollution and particularly urban air pollution, is associated with potentially severe adverse effects on human health, a thorough assessment of which is nevertheless still needed [7]. A number of recent studies have found a relation between mortality [8–10], respiratory symptoms [11–14], or hospital admissions [15], and air pollution.

Even though there is ample evidence that air pollution is likely to be associated with acute health effects [16], methodological problems have not yet been solved [17], in particular those involving the measurement of actual human exposure [18], but they certainly need to be carefully addressed [19]. Because air pollution involves complex mixtures of chemical pollutants, and because actual exposure is difficult to assess with reasonable accuracy, it is extremely difficult to identify the main components of air pollution involved in major health effects. Obviously, identifying these main components is a prerequisite to efficacious and acceptable measures to control the adverse consequences of air pollution to health. Classifications of hazardous environmental chemicals have been proposed [20], but it remains to be established to what extent, if any, such classifications can prove helpful. Another issue to be solved is the selection of appropriate criteria to assess the adverse effects of air pollution on human health [21] as it is unsure to what extent episodic respiratory symptoms or long-term effects on the respiratory tract can be reliably used.

Even though it is beyond doubt that air pollution is detrimental to human health, it is certainly risky at the present time to propose a quantified assessment of the role played by air pollution in the morbidity and mortality of the general population [22,23].

DIOXIN AND RELATED COMPOUNDS

Halogenated aromatic hydrocarbons (HAHs) have aroused much concern in the public and scientific communities during the past decade. HAHs are highly lipophilic and resistant to degradation, and are therefore logically considered as hazardous to the environment. They include 75 polychlorinated dibenzodioxin isomers (dioxins), 135 polychlorinated dibenzofuran isomers (furans), and polychlorinated and brominated biphenyls (PCCs and PCBs, respectively). As some commercial PCB products as well as chlorophenoxy (e.g. 2,4-D or 2,4,5-T) herbicides were found to be contaminated with small amounts of dioxins and furans (e.g. 50 ppm of TCDD in some batches of 2,4,5-T), confusion often arose regarding the compound or mixture of compounds, which was actually involved; this may result, and has actually resulted, in erroneous conclusions regarding proven health consequences even though toxic equivalency factors and toxic equivalents were proposed [24]. For example, a number of studies investigated the effect of Agent Orange, a formulation containing 50% of

2,4,5-T used during the Vietnam war as a defoliant, and in many instances, conclusions on adverse effects for human health were drawn, as if dioxin as such was spread over both the Vietnamese population and the G.I.s. As this stage, it is absolutely essential to emphasize that toxic risks can only be assessed with certainty provided that human exposure has been reasonably measured and quantified, whatever the societal or psychological emphasis (see Chapter 3).

The manufacture of PCBs ceased in the late 1970s in many Western countries, but sources of contamination still exist today, such as waste incinerators, sludge, automobile engines, or cigarette smoke. Of these many compounds, 2,3,7,8-TCDD or the Seveso dioxin (later called "dioxin") received the most attention, even though it induced somewhat limited toxicities to exposed human beings, and in any case toxicities much less than those expected from animal studies or than the fears inappropriately triggered by the media. It is also noteworthy that the available information on these compounds was essentially gained with dioxin, so that very little is actually known of the potential adverse effects of dioxin-related compounds.

Dioxins are formed during the production of chlorinated organic solvents, hexachlorophene, and the herbicide 2,4,5-T, but the production of these compounds was either strictly controlled or banned. Extremely small quantities of dioxins can be present almost everywhere in the world, but supposedly at levels very often below currently available detection limits. When assessing the effects of such extremely low levels, it is mandatory (not to say fair) to keep in mind what a ppb (part per billion) or ppt (part per trillion) actually means in terms of actual exposure to human beings.

Data on the adverse health effects of dioxin and related compounds in man come from isolated clinical reports and epidemiological studies after uncontrolled accidental exposure in most instances. Acute exposure is associated with nausea and vomiting, headaches, irritation of the eyes, skin, and respiratory tract. Acneiform lesions or chloracne are by far the main significant complication of dioxin as well as PCB exposure in humans [3]. Chloroacne usually appears 1 to 3 weeks after exposure. In sharp contrast to animal studies, there is no firmly conclusive evidence that dioxin or related compounds are either neurotoxic, hepatotoxic, or teratogenic in humans. Similarly, dioxin is irrefutably an animal carcinogen and an immunotoxicant, but it has not been shown to conclusively exert such adverse effects in humans. The finding that the dioxin-resistant hamster is 5,000 to 10,000 times less sensitive than the mouse or the rat, suggests there is an unusually large interspecies variability as regards dioxin-induced toxic effects, and this should be taken into account when extrapolating animal data to human beings. Overall, it remains to be conclusively established whether the majority of toxic effects described in animals occur also in humans [24–29].

A number of epidemiological studies have focused on the human carcinogenicity of dioxin and related compounds and the results of these studies have been reviewed repeatedly with conflicting conclusions [30–36]. At the present

time, it seems impossible to reach a consensus on the potential of dioxin and related compounds as human carcinogens.

No firmly conclusive data is available to contradict the position that dioxin, at the current level of exposure in the general population, is extremely unlikely to be toxic [28]. Nevertheless, to take into account the remaining uncertainty, it appears prudent to limit human exposure to a minimum [24].

ENVIRONMENTAL TOBACCO SMOKE

Although it is well established that active cigarette smoking is a major cause of morbidity and mortality, the health consequences of involuntary exposure to tobacco smoke are still highly controversial [3,37,38].

Exposure to environmental tobacco smoke (ETS) is often referred to as passive smoking. It combines sidestream smoke which is released from the burning end of cigarettes and mainstream smoke exhaled by active smokers. Sidestream smoke contains more partial pyrolysis products, that is to say more toxic and carcinogenic substances than mainstream smoke, but concentrations are markedly reduced by dilution in the room air, so that exposure of involuntary smokers is lower. Assessing actual exposure to ETS is extremely difficult and has become a major cause for current controversies when interpreting results of both positive and negative studies [39]. Obviously, the use of spouse smoking data alone does not cover exposures outside the home. In addition, it is unclear whether other conditions of exposure are actually relevant. One major problem with ETS is that societal and economic biases quite often confound the results obtained.

Asthma and the increased occurrence of respiratory infections are the main adverse effects associated with ETS in children [3]. However, the only clear link is between maternal smoking and children less than one year of age, probably because exposure to maternal smoking is markedly higher. In adults, no consistent link has been found [40,41]. Following early reports published in 1981 that lung cancer risk may be increased in nonsmoking women married to smokers, this association has been extensively examined and to date provides only indirect, if any, evidence of a causative relationship. Interestingly, most available results have been interpreted as showing an increased lung cancer risk consistent with results from studies in direct smokers and also with the worldwide trend to curb smoking in the general population. However, few studies provide evidence that ETS is associated with increased lung cancer while a number of studies obtained negative results. As regards cancers at other sites, there is no clear evidence that passive smoking is associated with an increased risk despite early and unconfirmed results.

A few studies have examined the consequences of passive smoking on cardiovascular diseases. Glantz and Parmley [42] suggested that passive smoking might increase the risk of cardiovascular diseases by promoting atherogenesis, increasing platelet aggregation and thrombosis, reducing the oxygen-carrying capacity of the blood and altering myocardial metabolism.

ASBESTOS AND MAN-MADE MINERAL FIBERS

Natural (asbestos) and man-made mineral fibers [43–46] are widely used for their heat, electrical and acoustic insulating properties, and to add strength to cement products, or reinforce brake shoes. Asbestos is a generic name given to a group of highly fibrous minerals that are hydrated silicates of magnesium and iron, of which six are of commercial importance: one serpentine mineral called chrysotile ("white asbestos"), and the amphiboles, amosite ("brown asbestos"), crocidolite ("blue asbestos"), anthophyllite, tremolite, and actinolite.

Asbestos fibers must gain access to the body to cause disease [45]. As they do not pass through the skin, inhalation is the main route of entry. Absorption of asbestos fibers by the gastrointestinal tract is possible, but the fate of absorbed fibers is still a matter of debate. The US Environmental Protection Agency proposed a maximal contamination level for asbestos in drinking water of 7 million fibers longer than 10 μm per liter. As high exposure to asbestos was associated mainly with mining and milling of raw material, the majority of available data on human exposure and related adverse consequences derives from studies in highly exposed workers.

The adverse effects of asbestos exposure [45] include the deposition of fibres at various thoracic sites, tumours of the pleura and peritoneum (mesothelioma), and lung cancer [47]. The fibrous lung disease associated with asbestos, a characteristic pneumoconiosis called asbestosis, has been known since the early years of this century. Asbestosis is mainly a disease of occupational origin. The severity of the lung reaction is correlated with both the duration and intensity of exposure. Although cases have resulted from intense exposure of one day duration, clinical manifestations typically appear after 20 to 40 years of occupational exposure. The classical picture of asbestosis includes a history of significant asbestos exposure, X-ray evidence of lung fibrosis, reduced FVC, end inspiratory rates, and diffusing capacity. Diagnosis can be confirmed by demonstrating asbestos bodies in biopsies or bronchoalveolar lavage. Although lung cancer is the most frequent fatal complication of asbestos in exposed workers, primary cancer (mesothelioma) of the pleura or peritoneal membrane is often considered as a hallmark of asbestos exposure. Indeed, a history of asbestos exposure can be identified in more than 85% of malignant mesothelioma. Asbestos-associated mesotheliomas appear to occur after lower exposure than asbestosis or lung cancer, but typically the latency period is long, or extremely long, up to 57 years. Smoking greatly increases the risk of asbestos-associated lung cancer, but not of mesothelioma.

It is however unclear how asbestos can cause cancer [45]. Immune changes, particularly impaired cell-mediated immunity [26], have been described, but it is doubtful that they can play a critical role. That chrysotile fibers may be less carcinogenic than other asbestos fibers has been advocated, but remains to be firmly established. This is as yet a highly debated issue, not devoid of economic and political considerations. Attempts have been made to link asbestos exposure to tumours at other sites, for instance the gastrointestinal tract, but these

are poorly justified.

Another issue of concern is the risk from asbestos in the indoor air [43,45]. In many industrialised countries, regulatory agencies have restricted, then banned, asbestos-containing materials in public buildings. Asbestos is widespread in a number of private homes. However, a major problem is to assess the actual risk of indoor asbestos for human health. Estimation of risk has so far been based on a non-threshold assumption for asbestos-related carcinogenicity, an assumption that is highly debated. Based on this assumption, an extremely high number of deaths due to cancer related to indoor asbestos has been predicted to occur in the forthcoming decades. However, it should be kept in mind that such a prediction may be, scientifically speaking, as accurate and reliable as a weather report covering the whole of next year! A further point to be made is that clearing asbestos from buildings may cause even more problems because of increased exposure. It is therefore essential when considering asbestos removal, to take into account a number of factors such as the shape of asbestos fibers, the technical accessibility of the fibers and so on.

Another major issue is that no, or extremely little, information is available on the adverse effects of new insulating materials. Even though claims have been made that no adverse effects should be expected from exposure to these materials [46], it is unfortunate that they are based on evidence as fragile as that used to indicate that indoor asbestos exposure is detrimental to human health. Whatever the actual risk of asbestos and other man-made mineral fibers, it is beyond doubt at the present time, that exposure to substitute fibers should be carefully monitored to assess potential toxicological hazards.

RADON

Radon is another major current concern related to adverse effects associated with indoor pollution [48,49]. Radon gas is derived from the radioactive decay of radium, an ubiquitous element found in rock and soil. Radon can easily diffuse through air and is soluble in water. It tends to accumulate in enclosed structures like mines and buildings. The major route of exposure to radon is inhalation. In further agreement with 19th century studies, modern epidemiological studies in exposed workers, essentially uranium miners (e.g. those from mines of the Colorado plateau), unequivocally showed that radon can cause lung cancer.

Evidence of an association between radon exposure in the home and excess lung cancer is far more controversial, even though studies suggested a statistically significant association between bronchial cancer and estimated exposure to radon in dwellings [50,51]. Nevertheless, assumptions that radon exposure may result in 7,000 to 30,000 annual deaths in the United States, should still be considered as theoretical. That extrapolation from high exposure levels in the miners to low exposure in home dwellers is valid has never been proved [52].

As with asbestos-related lung cancer, there is a major need to provide conclusive evidence that radon carcinogenicity is linearly related to exposure, without a threshold.

VOLATILE ORGANIC COMPOUNDS

Modern houses in industrialised countries are generally contaminated with a wide array of potentially toxic organic compounds.

Formaldehyde was extensively used as a preservative or fixative. One very common application has been in urea-formaldehyde foam insulation which generates free formaldehyde in the built environment, with associated clinical complaints due to its irritant and allergenic properties at extremely low levels of 0.1 or even 0.02 ppm (see Chapter 25).

Solvents should be considered as domestic hazards. Because of their lipophilicity, all solvents are capable of producing CNS sedation. Benzene is the simplest member of aromatic hydrocarbons recovered from the refinery processing of crude petroleum. Its largely primary use is nowadays as an intermediate in the production of other chemicals. Benzene is an excellent solvent, but it was largely banned for this use because of major hematological toxicity resulting in abnormalities of the three blood cell lines and more importantly and conclusively in leukemia [53]. Typically, benzene-associated leukemias develop within 5 to 15 years of exposure. A major recent concern derives from the presence of benzene in significant quantity in lead-free gas, which has unfortunately been advertised as "green gas" in many countries, sometimes with the support of government fundings. In most settings, the maximally accepted contaminant level is 1 ppm or even less (for instance 5 ppb in drinking water) but higher levels are commonly found in lead-free gas. However, it should be kept in mind that other aromatic hydrocarbons, notably toluene and the xylenes, can be found in measurable amounts in the air of major cities of the Western as well as the developing world. It remains to be established what is the actual risk for human health of exposure to such levels. Again, a major concern is related to the occurrence of more frequent cancers, but no general consensus does exist regarding whether a safe level of exposure can be identified with carcinogenic substances such as benzene [54].

Although the acute toxicity of ethylene glycol is well established and has been addressed elsewhere in this volume (see Chapter 24), there have been no reports of adverse health effects from chronic environmental exposures. Propylene glycol was classified as a "Generally Recognized As Safe" (GRAS) substance by the US FDA.

Also called dibromethane, methylene chloride is a clear, colourless liquid with a mild, sweet odour. This is an excellent solvent with many industrial and domestic applications. The major adverse health effects of short-term exposure include central nervous system depression resulting in unconsciousness and coma at concentrations above 8,000 ppm. Strong irritation of the eyes, the skin,

and the upper respiratory tract, cardiac effects including myocardial ischemia and dysrhythmia, and rarely pulmonary edema can be seen. The specific consequences of chronic exposure, if any, have not been fully determined.

N-hexane and methyl n-butyl ketone are neurotoxic and can induce peripheral neuropathy. In contrast to rodent studies, no epidemiological evidence of hepatic damage associated with 1,1,1-trichloroethane and trichloroethylene, is available.

PESTICIDES

Due to their ever expanding use, pesticides are a major concern of potential environmental hazards. Interestingly, epidemiological studies have suggested that pesticide exposure may be associated with more frequent malignancies, mainly lymphomas [55]. However, while available data indicate that lymphomas are likely to be more frequent among those people living in rural areas, it remains to be firmly established to what extent, if any, pesticide exposure is involved.

Aldicarb, a carbamate derivative, was reported to exert the highest acute toxicity among pesticides in rodents (as evidence by the LD_{50}). Concern arose when housewives exposed to aldicarb contaminated communal drinking water were found to have a decreased $CD4^+/CD8^+$ T lymphocyte ratio similar to that evidenced in AIDS patients and the media was too prone to suggest that a cause of chemical AIDS had been identified. Rodent studies failed to confirm any adverse effects of aldicarb on the immune system [27].

Overall, pesticides are certainly a major cause of acute poisonings, particularly in developing countries. It remains to be established to what extent pesticides can contribute to adverse chronic effects in humans following low-level exposure.

MICROWAVES AND ELECTROMAGNETIC FIELDS

Man-made electromagnetic fields have become a part of our local environment and recently they have been a cause of increasingly acute concern from the public, resulting in many position papers from both the scientific community and regulatory agencies, as electromagnetic radiations were found to cause damage to the body by both ionizing and non-ionizing mechanisms [56].

Electromagnetic radiation consists of energy waves moving through space at the speed of light and accompanied by a vibrating magnetic field. It should be remembered that electromagnetic fields are a natural feature of our environment. The sun radiates electromagnetic fields in the infrared, visible and ultraviolet regions, and cosmic rays are another source of electromagnetic radiation. However, man is exposed to an ever-increasing range of electromagnetic frequencies used for radar, television, radio, as well as military and other

forms of communication. The other main man-made source of electromagnetic fields is power distribution and use. Therefore, the question as to whether extremely low frequency electromagnetic fields pose a health risk is of critical importance.

The primary effect of microwaves is thermal injury. The first well-controlled study linking cancer and electromagnetic field exposure was reported in 1979. Later on, several studies demonstrated an increased relative risk of several malignancies, mainly brain tumours and leukemias, associated with exposure to electromagnetic fields. However, the relative risk was below 2.0 in most studies and also no association between electromagnetic fields and leukemia was reported by several authors. Interestingly, the results of several large epidemiological studies were recently published and these supported the association.

CONCLUSION

In the recent past, drug-induced side-effects as well as adverse effects related to occupational exposure have been increasingly well identified, recognized, and analysed. Therefore, the safety profile of pharmaceutical products and chemical exposure at the workplace is more and more accurately and thoroughly delineated.

This is certainly not so, however, as far as the exposure to a wide array of potentially hazardous substances, either via the outdoor or the indoor air, is concerned. It has been claimed that epidemiological methods are not sensitive enough to help reach widely accepted conclusions [57], and this may explain why environmental issues related to human health have been so vividly brought to light, as the media found in assumptive results of published studies, sufficient ground to arouse public concern that the scientific community could hardly counteract due to the lack of clearly negative results. This unfortunate situation demonstrates to what extent a discipline such as environmental medicine is now necessary to ensure that health issues related to environmental exposures can be dealt with, both objectively and open mindedly. It is beyond doubt that toxicologists and among them, human (or clinical) toxicologists, can be of help in this context.

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Index

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