T E Peck
M Williams

Pharmacology for Anaesthesia and Intensive Care

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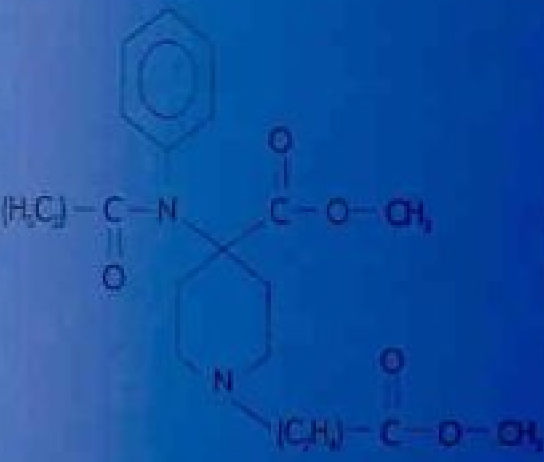
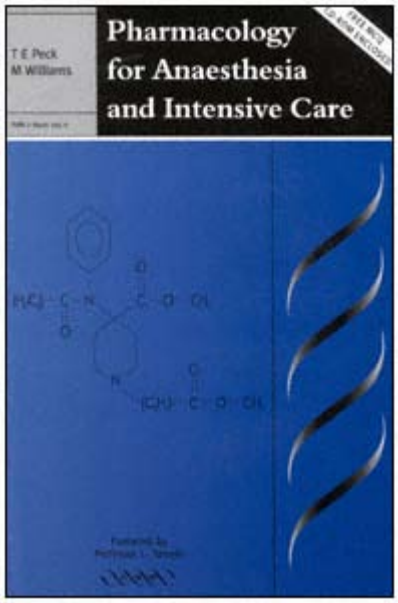


Foreword by
Professor L. Strunin



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Pharmacology for Anaesthesia and Intensive Care

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PREFACE

This book has been written with three groups of people in mind. Firstly, those preparing for the FRCAespecially the primary exam, but also for those wishing to brush up on pharmacology for the Final. Secondly, for those physicians involved in intensive care who are from other disciplines, and thirdly the large cohort of people who are involved in the care of patients in theatre and intensive care who want a greater understanding of the pharmacology involved.

For those preparing for the FRCA the choice of books previously available fell between the large, comprehensive (and expensive!), and the small 'pocket' books that did not attempt to cover the basic principles of pharmacology. In just over 300 pages, we have attempted to produce a comprehensive text of the basic principles and drugs used in Anaesthesia and Intensive Care, together with a proven means of self assessmenta QBase CD-ROM, containing 365 MCQs. Every attempt has been made to ensure that all the answers can be found within the book itself. Each MCQ has also been referenced to external sources which may provide a greater depth than is practical within the scope of this book.

We have sought to minimise repetition, while retaining a comprehensive discussion of individual drugs that incorporates a degree of 'compare and contrast'. We have kept a similar format throughout the book wherever possible, which should facilitate learning and searching for specific information. Some of the information included may seem a trifle obscure to some, but is there simply because it has been asked in the MCQ section of the FRCA examinations in the recent past.

We should like to thank Dr. Sue Hill (MA, Ph.D., FRCA) for her most helpful comments and corrections of the text at the many stages of its creation.

TP
MW

JANUARY 2000

To Rebecca and our three daughters,
Hannah, Emmie and Sophie
TP

To my parents and to Emily
MW

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FOREWORD

I can recall, many years ago, being asked, rather hesitantly, by a Senior Lecturer in pharmacology if he could come and watch an anaesthetic? No problembut I wondered why? He watched in rapt, silent, attention as I injected the thiopentone at the start of the anaesthetic. The patient duly fell asleep. My visiting pharmacologist looked at the asleep patient and then spoke for the first time. "My God, it works!" He had lectured for twenty years on anaesthetic drugs but had never seen one given in clinical practice.

Anaesthesia and intensive care medicine (ICM) involve the regular administration of potent drugs to patients by routes intended to raise their concentration at their active sites as quickly as possible. We often need an immediate response. However, all potent drugs have unwanted effects. In addition, they are not always predictable. In this context, it has always seemed to me to be good advice to not give a drug with an immediate action unless one has the knowledge and necessary skills to deal with all possible events that might follow. How to acquire this knowledge and skills?

The Faculty of Anaesthetists was formed within the Royal College of Surgeons of England at the inception of the National Health Service (NHS) in 1948. The prime task of the Faculty was to run a Fellowship examination (FFARCS) for the specialty. Right from the start, pharmacology was a core topic for examination in the FFARCS. Today the Royal College of Anaesthetists oversees a comprehensive, seven year [two years as a senior house officer and five years as a specialist registrar (SpR)] training programme in anaesthesia and ICM. The Fellowship examination is an integral part of the training programme testing knowledge at two stages. The Primary examination has pharmacology as one of its key components. Passing the Primary probably determines whether a doctor will go on to be a professional anaesthetist as it is part of the requirements to enter the SpR grade. The Final examination, which also includes applied pharmacology as well as ICM, determines passage to the last years of the SpR training and obtaining the certificate of completion of specialist training (CCST). This certificate allows entry to the Specialist Register of the General Medical Council and eligibility for a consultant appointment in the NHS.

Thus we can see that pharmacology is intimately woven into the training of anaesthetists. However, knowledge requires access to information. This book contains a concise account of the necessary pharmacology required for the Fellowship examinations. Trainees, naturally, tend to see examinations as hurdles and not always immediately related to their clinical practice. Nevertheless they will spend their professional lives giving drugs and it is clearly in the patients' best interests as well as the doctors' that the latter has all the necessary knowledge and skills so that the former can benefit and not be harmed.

Those interested in education sometimes say that reading by itself, particularly when attempting to memorise facts for an examination, may not be the best way for permanent knowledge acquisition. However when one studies why trainees fail examinations, lack of knowledge is a key factor. In addition, difficulty in answering multiple choice questions (MCQs) is another common cause of failure in the Fellowship. The CD-ROM which accompanies this book allows the reader to test their knowledge acquisition and practice their MCQ technique.

Drs Peck and Williams are practicising anaesthetists at the start of their careers. Unlike my Senior Lecturer colleague they have 'been there, done it and are busy acquiring the T-shirt'. This book reflects their experience of drugs used in anaesthesia and ICM and links this with the basic pharmacology included in the text. As they point out in their Preface, anaesthetists will benefit in regard to the Fellowship examinations, as will the increasing number of non-anaesthetists involved in ICM who need to know about anaesthetic drugs. As I have indicated above, anaesthesia training has always recognised the central role of pharmacology. Today, other disciplines need to follow this lead. A good start would be to use this book and the accompanying CD-ROM.

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JANUARY 2000

LIST OF ABBREVIATIONS USED

ACE	angiotensin converting enzyme
cAMP	cyclic adenosine monophosphate
cATP	cyclic adenosine triphosphate
cADP	cyclic adenosine diphosphate
AV	atrio-ventricular
bd	twice per day
BDZ	benzodiazepine
BP	blood pressure
Cl	clearance
CNS	central nervous system
CO	cardiac output
CSM	Committee on Safety of Medicines
CT	computerised tomography
Da	dalton
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
EEG	electroenecephalogram
ECG	electrocardiogram
ECT	electroconvulsive therapy
FRC	functional residual capacity
GABA	gamma aminobutyric acid
cGMP	cyclic guanosine monophosphate
h	hour
HR	heart rate
ICP	intracranial pressure
INR	international normalized ratio
IOP	intraocular pressure
IVC	inferior vena cava
LVF	left ventricular failure

m	meter
MAO	monoamine oxidase
MI	myocardial infarction
min	minute
N2O	nitrous oxide
nm	nanometer
NO	nitric oxide
O2	oxygen
PaCO2	carbon dioxide tension
PaO2	oxygen tension
PDE	phosphodiesterase
ppm	parts per million
RNA	ribonucleic acid
s	second
SA	sino-atrial
SVR	systemic vascular resistance
TXA2	Thromboxane A2
Vd	volume of distribution
v/v	volume (of solute) per volume (of solvent)
SVT	supraventricular tachycardia
tds	three times per day
VT	ventricular tachycardia
V/Q	ventilation/perfusion
5-HT	serotonin

QBASE:
MCQS IN PHARMACOLOGY FOR ANAESTHESIA AND INTENSIVE CARE

QBase: MCQs in Pharmacology for Anaesthesia and Intensive Care contains the latest version of the QBase Interactive MCQ Examination software and is released in conjunction with *Pharmacology for Anaesthesia and Intensive Care.*

The questions have been compiled from the pharmacology sections of other QBase Anaesthesia publications with the addition of new questions to reflect the content of the book and recent developments in drug therapy of relevance to anaesthesia. The questions have been re-edited in conjunction with Tom Peck and Mark Williams to complement the material in their book. They have been designed to both test knowledge of pharmacology for the Primary FRCA as well as assist revision by providing comprehensive answers and references for further reading.

The CD-ROM contains 365 multiple-choice questions divided into 8 main subjects. As with other titles in the QBase series, it contains a series of pre-formatted mock exams that may be accessed through the exam buttons on the quick start menu. Each mock exam contains 25 questions. Using the "Autoset an Exam" button on the main menu you can generate further mock exams of 25 questions chosen at random from the entire question set. Candidates wishing to make up their own exam for either revision or assessment can also use the "Create your own exam" option on the main menu.

The QBase CD-ROM was originally designed to allow FRCA candidates to analyse how their guessing strategy affects their performance in MCQ examinations, but this feature will no doubt be of great interest to anyone undertaking the MCQs to assist their own learning. Negative marking is employed by the examination analysis software, to match the FRCA examination. Candidates sitting the

FRCA or a similar examination should remember that negative marking in MCQ examinations was designed to nullify the effects of random guesses, which have an equal chance of being right or wrong, and not to penalise candidates. Our experience in teaching MCQ technique to candidates sitting such an exam suggests that the advice "do not guess" is incorrect. Candidates are consistently surprised at the positive benefits of educated and wild guesses. Whilst not a substitute for knowledge and proper preparation for the exam, the assessment of exam technique can provide valuable feedback on an individual's strategy which may lead to improved performance in the exam. It should be used repeatedly to optimise exam technique.

We hope that candidates will find the combination of this book and CD-ROM a useful adjunct to their own learning and revision.

EDWARD HAMMOND
ANDREW MCINDOE
QBASE SERIES DEVELOPERS/EDITORS

JANUARY 2000

RUNNING THE QBASE PROGRAM ON CD-ROM

System Requirements

An IBM compatible PC with a minimum 80386 processor and 4MB of RAM VGA Monitor set up to display at least 256 colours.

CD-ROM drive

Windows 3.1 or higher with Microsoft compatible mouse

The display setting of your computer must be set to display "SMALL FONTS".

See Windows manuals for further instructions on how to do this.

Installation Instructions

The program will install the appropriate files onto you hard drive. It requires the QBase CD-ROM to be installed in the D:\drive.

In order to run QBase the CD-ROM must be in the drive.

Print Readme.txt and Helpfile.txt on the CD-ROM for fuller instructions and user manual

Windows 95/98

1. Insert the QBase CD-ROM into drive D:

2. From the Start Menu, select the RUN option

3. Type D:\setup.exe and press enter or return

4. Follow the Full Installation option and accept the default directory for installation of QBase.

The installation program creates a folder called QBase containing the program icon and another called Exams into which you can save previous exam attempts.

5. To run QBase double click the QBase icon in the QBase folder. From windows Explorer double click the QBase.exe file in the QBase folder.

Windows 3.1/Windows for Workgroups 3.11

1. Insert the QBase CD-ROM into the drive D:

2. From the File Menu, select the RUN option

3. Type D:\setup.exe and press enter or return

4. Follow the instruction given by the installation program. Select the Full Installation option and accept the default directory for installation of QBase

The Installation program creates a program window and directory called QBase containing the program icon. It also creates a directory called Exams into which you can save previous attempts.

5. To run QBase double click on the QBase icon in the QBase program. From File Manager double click the QBase.exe file in the QBase directory.

SECTION 1
BASIC PRINCIPLES

1
Drug Passage Across the Cell Membrane

Many drugs need to pass through one or more cell membranes to reach their site of action. A common feature of all cell membranes is a phospholipid bilayer, about 10 nm thick, arranged with the lipophilic chains facing inwards. This gives a sandwich effect, with two hydrophilic sides surrounding the central lipophilic layer. Within the layer are glycoproteins, which may act as ion channels, receptors or enzymes. The cell membrane has been described as a 'fluid mosaic' as the positions of individual phosphoglycerides and glycoproteins are by no means fixed (Figure 1.1).

The general cell membrane structure is modified in certain tissues to allow more specialized functions. Capillaries have fenestrae, which are regions of the membrane where the outer and inner cell layers are fused together, with no intervening cytosol. This renders the capillaries relatively permeable and, in particular, fluid can pass rapidly through the cell by this route. In the case of the basement membrane of the glomerulus, gaps or clefts exist between cells to allow the passage of larger molecules as part of filtration. Tight junctions exist in the bloodbrain barrier (BBB), intestinal mucosa and renal tubules. They limit the passage of certain molecules and also prevent the lateral movement of glycoproteins within the cell membrane, which may help to keep specialized glycoproteins at their site of action (e.g. transport glycoproteins on the luminal surface of intestinal mucosa) (Figure 1.2).

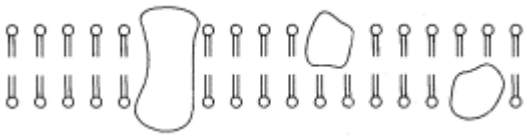


Figure 1.1:
Representation of the cell membrane structure.
The integral proteins embedded in this phospholipid bilayer may be receptors, enzymes or ion channels.

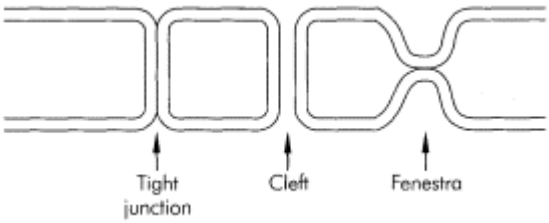


Figure 1.2:
Modifications of the general cell membrane structure.

Methods of Crossing the Cell Membrane

Passive Diffusion

This is the commonest method for crossing the cell membrane. Drug molecules move down a concentration gradient, from an area of high concentration to one of low concentration, and the process requires no energy to proceed. The unionized form of the drug is lipid-soluble and diffuses easily by dissolution in the lipid bilayer. (Factors influencing the rate of diffusion are discussed below.)

In addition, there are specialized ion channels in the membrane that allow facilitated passage for certain molecules. When opened, ion channels are often involved in rapid ion flux for a short duration (a few milliseconds) down relatively large concentration and electrical gradients, which makes them suitable to propagate the voltage-gated action potential or muscle membrane potential.

The acetylcholine (ACh) receptor has five subunits arranged to form a central ion channel that spans the membrane. Of the five subunits, two (the a subunits) are identical. The receptor requires the binding of two ACh molecules to open the ion channel, allowing ions to pass at about 107 s1. If a threshold flux is achieved, depolarization occurs, which is responsible for impulse transmission. The ACh receptor demonstrates selectivity for small cations, but it is by no means specific for Na+ (Figure 1.3).

Ion channels may have their permeability altered by natural molecules or by drugs. Local anaesthetic binds to the internal surface of the fast Na+ ion channel and prevents the conformational change required for activation, while non-depolarizing muscle relaxants prevent receptor activation by competitively inhibiting the action of ACh.

Facilitated Diffusion

Facilitated diffusion refers to the process by which molecules combine with plasma proteins to cross the membrane. The rate of diffusion of the moleculeprotein complex is faster than that which would be expected by diffusion alone,

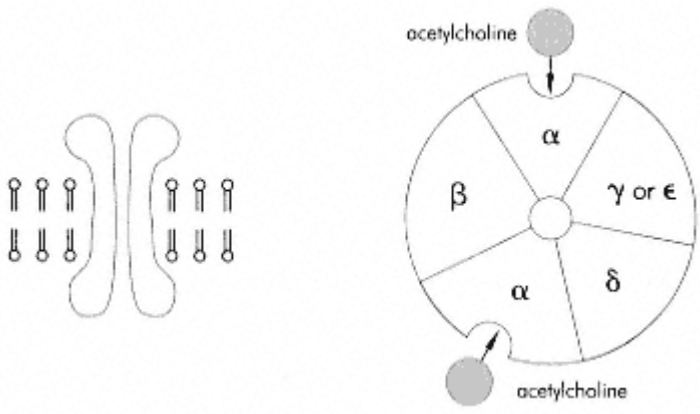


Figure 1.3:
The acetylcholine (ACh) receptor has five subunits and spans the cell membrane. ACh binds to the a subunits, causing a conformational change and allowing the passage of small cations through its central ion channel.

and the bond is reversible. Examples of this process include the absorption of steroids and amino acids from the gut lumen. The absorption of glucose, a large and polar molecule, would be expected to be slow if transferred by diffusion alone, and it requires facilitated diffusion to cross membranes (including the BBB) at a sufficient rate.

Active Transport

Active transport is an energy-requiring process. The molecule is transported against its concentration gradient by a pump, which requires energy to function. Energy can be supplied either directly to the ion pump, or by relying on an ionic gradient (which itself needs energy to sustain the presence of a gradient against the steady state equilibrium.)

Na+/K+ ATPase is an example of an active pumpthe energy in the high-energy phosphate bond is lost as the molecule is hydrolysed, with concurrent ion transport against the respective concentration gradients. It is an example of an antiport, as substances are moved in different directions. The Na+/amino acid symport (substances moved in the same direction) in the mucosal cells of the small bowel is an example of secondary active transport. Here, amino acids will only cross the membrane of the mucosal cells when Na+ is bound to the carrier protein and flows down its concentration gradient (which is generated using Na+/K+ ATPase). So, directly and indirectly, Na+/K+ ATPase is central to active transport (Figure 1.4).

Active transport is more specific for a particular molecule than is the process of simple diffusion and is subject to specific antagonism and blockade. In addition, the fixed number of active transport binding sites may be subject to competition or saturation.

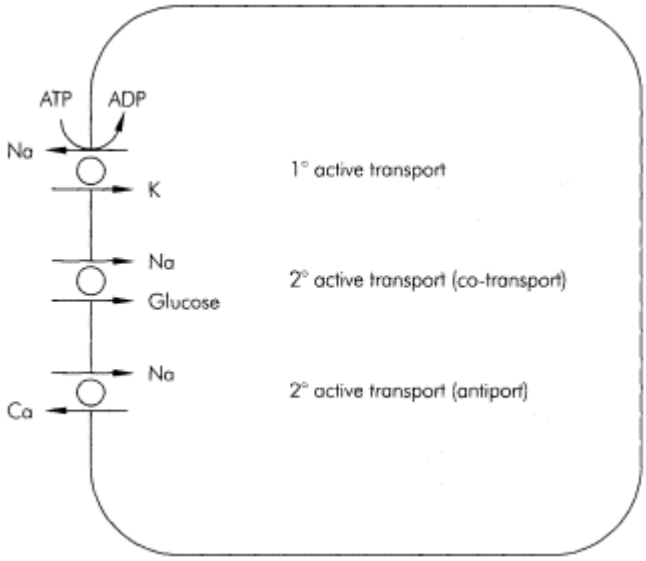


Figure 1.4:
Mechanisms of active transport across the cell membrane.

Pinocytosis

Pinocytosis is the process by which an area of the cell membrane invaginates around the (usually large) target molecule and moves it into the cell. The molecule may then be retained in the cell or may remain in the vacuole so created, until the reverse process occurs on the opposite side of the cell.

The process is usually used for molecules that are too large to traverse the membrane easily via another mechanism. Examples of this include the absorption of the large vitamin molecules (Figure 1.5).

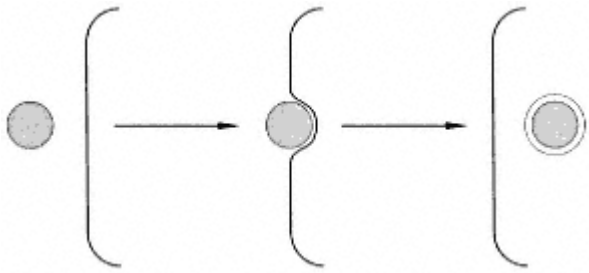


Figure 1.5:
Pinocytosis.

Factors Influencing the Rate of Diffusion

Molecular Size

The rate of diffusion is inversely proportional to the square root of molecular size (Graham's Law). Thus, small molecules (if other factors are equal) will diffuse much more readily than large ones. The molecular weights of anaesthetic agents are relatively small and, in practice, anaesthetic agents diffuse rapidly through lipid membranes.

Concentration Gradient

Fick's Law states that the rate of transfer across a membrane is proportional to the concentration gradient across the membrane. Therefore, increasing the plasma concentration of the unbound fraction of drug will increase its rate of transfer across the membrane and will accelerate the onset of its pharmacological effect.

Ionization

The lipophilic nature of the cell membrane only permits the passage of the unionized fraction of a drug. The degree to which a drug is ionized in solution depends on both the drug and the pH of the solution in which it is dissolved.

The pharmacological property of a drug that determines its degree of ionization in a given solution is the pKa. This is equivalent to the pH at which the drug is half ionizedthus, the concentrations of ionized and unionized portions are equal. pKa does not depend on whether a drug is acidic or basic (which is a fundamental property of the molecular structure).

The HendersonHasselbalch equation is most simply expressed as:

$$\mathrm{pH} = \mathrm{pKa} + \log \frac{[\text{proton acceptor}]}{[\text{proton donor}]}$$

Hence, for an acid (XH), the relationship between the ionized and unionized forms is given by:

$$\mathrm{pH} = \mathrm{pK_a} + \log \frac{[X^-]}{[XH]},$$

with X being the ionized form of an acid.

For a base (X), the corresponding form of the equation is:

$$\mathrm{pH} = \mathrm{pK_a} + \log \frac{[X]}{[XH^+]}$$

with XH+ being the ionized form of a base.

If considered this way, rather than using the terms acid and base in the equations themselves, the degree of ionization of a molecule may be simply established if its nature, pKa and ambient pH are known.

Bupivacaine is a base as it has a nitrogen atom, which accepts a proton to become ionized. As its pKa = 8.1, it is 83% ionized at physiological pH.

Aspirin is an acid with a pKa = 3.0. It is almost wholly ionized at physiological pH, although in the highly acidic environment of the stomach it is essentially unionized, which therefore facilitates its absorption. However, due to the limited surface area within the stomach more is absorbed in the small bowel.

Lipid Solubility

The lipid solubility of a drug reflects its ability to pass through the cell membrane. However, a high lipid solubility does not necessarily result in a rapid onset of action. Alfentanil is nearly seven times less lipid-soluble than fentanyl, yet it has a more rapid onset of action by virtue of a low pKa (alfentanil = 6.5; fentanyl = 8.4), so that at physiological pH a much greater fraction is unionized and available to cross membranes.

Lipid solubility affects the pharmacokinetics of absorption from a particular site. Thus, fentanyl is suitable for transdermal application as its high lipid solubility results in effective transfer across the skin. Intrathecal diamorphine readily dissolves into, and fixes to, the local lipid tissues, whereas morphine remains in the cerebrospinal fluid for longer, and is therefore liable to spread cranially, with an increased risk of respiratory depression.

Protein Binding

Only the unbound fraction of drug in plasma is free to cross the cell membrane. In practice, the theoretical considerations are of importance only if the drug is highly protein-bound. In these cases, small changes in the degree of binding produce large changes in the fraction of unbound drug.

Albumin or globulins may bind drugs. Albumin binds neutral or acidic drugs, and globulins (largely a1 acid glycoprotein) bind basic drugs.

Albumin has two binding sitesI and IItermed the warfarin and diazepam site respectively. Binding is usually readily reversible, and competition for binding between different drugs can alter the active unbound fraction of each. Furthermore, binding is possible at sites on the molecule distant to the diazepam and warfarin sites, but which may cause a conformational or ionic change to the molecule, which alters subsequent binding at these sites.

Though a1 acid glycoprotein is the predominant molecule that binds basic drugs, other globulins have an important function in binding individual ions and

molecules, particularly the metals. Thus, iron is bound to b1 globulin and copper to a1 globulin.

Protein binding is altered in a range of pathological conditions. Inflammation changes the relative proportions of the different proteins. The level of albumin falls in any acute infective or inflammatory process, independently of the effects of hypoalbuminaemia through liver impairment or protein loss. In conditions of severe hypoalbuminaemia (end-stage liver cirrhosis or burns), the proportion of unbound drug increases markedly such that the same dose will have a greatly exaggerated pharmacological effect. While the direction of effects may be predictable, the magnitude may be harder to estimate, and drugs should be titrated slowly against clinical effect.

2
Absorption, Distribution, Metabolism and Excretion

Absorption

Drugs may be given by a variety of routes. The particular route chosen will depend on whether the intended site of action is local or systemic, as well as considering the individual nature of the drug or patient. Both drug and patient factors affect absorption.

The oral route of administration may be considered to be local as well as systemic, e.g. vancomycin used to treat pseudomembranous colitis is acting locally; antacids also act locally in the stomachindeed systemic absorption may result in side-effects.

In general, the intravenous route provides the most reliable method of drug delivery as it does not rely on the integrity of gastrointestinal absorption, or on adequate skin or muscle perfusion. However, there are disadvantages to using this route. Pharmacological preparations for intravenous therapy are generally more expensive than the corresponding oral route, and the high plasma level achieved with some drugs may cause undesirable side-effects. In addition, central venous access is not without risk. Nevertheless, most drugs used in intensive care are given by intravenous infusion.

Oral

For a drug to be absorbed it must pass through the lipid membrane of the gut mucosa. Only unionized drugs pass readily through the lipid membrane of the gut, and thus the nature of the drug determines the site of absorption.

Acidic drugs (e.g. aspirin) are unionized in the highly acidic medium of the stomach, and therefore are absorbed more rapidly than basic drugs. Of the basic drugs, those that are weak bases (e.g. propranolol), though ionized in the stomach, are

relatively unionized in the duodenum, and are therefore absorbed. Strongly basic drugs (e.g. glycopyrrolate) remain ionized even at duodenal pH and are therefore not absorbed.

In practice, even acidic drugs are predominantly absorbed from the small bowel, as the surface area for absorption is so much greater as a result of mucosal villi. The advantage of an acidic drug such as aspirin, however, is that initial absorption is relatively rapid, giving a short time of onset from initial ingestion.

Bioavailability

Bioavailability is defined as the fraction of an oral dose reaching the systemic circulation, compared with a standard route of administration. This is usually the intravenous route, but another route may be used as a reference if the drug cannot be given intravenously. Bioavailability may be measured by plotting on the same graph curves of plasma concentration against time for an oral and intravenous bolus dose. Bioavailability is then given by the ratio of the areas under the respective curves (Figure 2.1).

Factors Influencing Bioavailability

• Pharmaceutical preparationthe preparation characteristics of a drug affect the absorption. If a drug is presented with a small particle size or as a liquid, dispersion is rapid. If the particle size is large, or binding agents prevent drug dissolution in the stomach, absorption may be delayed.

• Interactionsother drugs or food may interact and inactivate or bind the drug in question (e.g. the absorption of tetracyclines is reduced by the concurrent administration of Ca2+). In addition, other drugs may greatly increase first-pass metabolism by inducing hepatic enzymes,

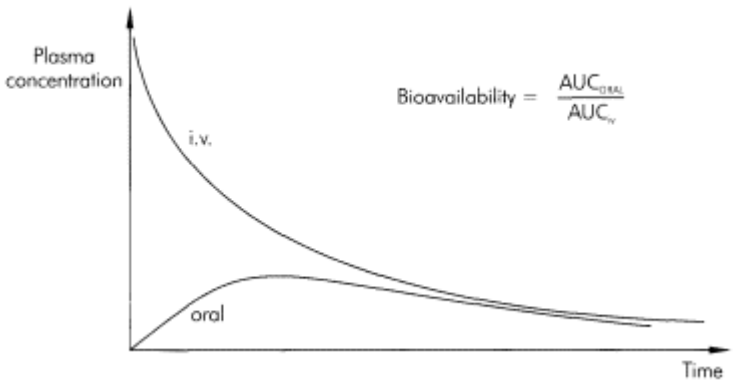


Figure 2.1:
Bioavailability may be estimated by comparing the areas under the curves.

resulting in a reduced bioavailability (e.g. phenobarbitone induces hepatic enzymes, reducing the oral bioavailability of warfarin).

• Patient factorsvarious patient factors affect absorption of a drug. The presence of congenital or acquired malabsorption syndromes, such as coeliac disease or tropical sprue, will affect absorption, and gastric stasis, whether as a result of trauma or drugs, slows the transit time through the gut.

• First-pass metabolismdrugs absorbed from the gut (with the exception of the oral and rectal mucosa) pass via the portal tract to the liver where they may be subject to first-pass metabolism. Metabolism at either the gut wall or liver will reduce the amount reaching the circulation. Therefore, an adequate plasma level may not be achieved orally using comparable doses. First-pass metabolism may be increased (see above) or decreased (e.g. cimetidine inhibits hepatic enzymes and may increase the oral bioavailability of propranolol).

Therefore, drugs with a high bioavailability are stable in the gastrointestinal tract, are well absorbed and undergo minimal first-pass metabolism (Figure 2.2).

Sublingual

The sublingual, nasal and buccal routes have two advantagesthey are rapid in onset and avoid the portal tract, being absorbed directly though the mucosa into the bloodstream. This is advantageous for drugs where a rapid effect is required, e.g. glyceryl trinitrate (GTN) spray for angina, or sublingual nifedipine for the relatively rapid control of high blood pressure.

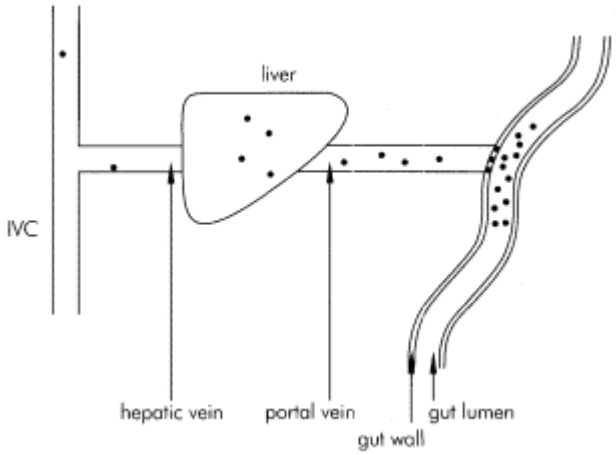


Figure 2.2:
First-pass metabolism may occur in the gut wall or in the liver to reduce the amount of drug reaching the circulation.

Rectal

The rectal mucosa is another route used to avoid first-pass metabolism, and may be used if the oral route is prohibited. However, drugs may also be given rectally for their local effects (e.g. steroids for inflammatory bowel disease), as well as their systemic effects (e.g. diclofenac suppositories for analgesia). There is, however, no evidence that the rectal route is more efficacious than the oral route. Indeed, the rectal route provides a relatively small surface area, and absorption may be slow or incomplete.

Intramuscular

The intramuscular route avoids the problems of gastrointestinal instability, absorption and first-pass metabolism, so that absorption should be 100%. The speed of onset is more rapid compared with the oral route, and may well approach that of the intravenous route. It is important to note, however, that the profile of absorption may be sensitive to local perfusion at the site of injection. Injection at a poorly perfused site may result in delayed absorption and for this reason the well-perfused sites of deltoid, quadriceps or gluteus are preferred. In addition, if muscle perfusion is poor, due either to systemic hypoperfusion (hypovolaemia in trauma or haemorrhage) or local vasoconstriction (due to hypothermia following surgery) then an intramuscular injection will not be absorbed until muscle perfusion is restored.

Delayed absorption will have two consequences. First, the drug will not have its desired systemic effect, which may result in the administration of further doses. Second, if perfusion is subsequently restored, the plasma level may suddenly rise into the toxic range. For this reason, the intravenous route is preferred if there is any doubt as to the adequacy of perfusion, with repeated small intravenous doses being titrated to clinical effect.

Intramuscular injections may be painful (e.g. cyclizine) and may cause a local abscess or haematoma. They should not be used in the coagulopathic patient. In addition, there is the risk of inadvertent intravenous injection of drug intended for the intramuscular route.

Subcutaneous

This is a convenient route for the administration of drugs that cannot be given orally. Oral therapy may not be effective if the drug is destroyed in the stomach or undergoes extensive first-pass metabolism. Where patient compliance is a problem, depot preparations may be useful. Anti-psychotic medication and some contraceptive formulations have been used in this way.

As with the intramuscular route, the kinetics of absorption are dependent on local and regional blood flow, and may be markedly reduced in shock. Again, this has

the dual effect of rendering the (non-absorbed) drug initially ineffective, and then subjecting the patient to a rapid bolus once the perfusion is restored.

Certain preparations of insulin are designed to be absorbed slowly over hourshere co-preparation with zinc or protamine gives a slower absorption profile.

Transdermal

The transdermal route provides a useful method of avoiding first-pass metabolism, but may also be used to provide a topical effect. Thus, fentanyl and nitrates may be given for their systemic effects, and steroids may be given topically for a local effect, albeit with the attendant risks of systemic absorption. Factors favouring transdermal absorption are high lipid solubility, and a good regional blood supply to the site of application (therefore, the thorax and abdomen are preferred to limbs).

Local anaesthetics may be applied topically to anaesthetize the skin before venepuncture, skin grafts or minor surgical procedures. The two commonest preparations are topical EMLA and topical amethocaine. The first is a eutectic mixture of lignocaine and prilocaine, with each lowering the melting point of the other. Amethocaine is an ester-bonded local anaesthetic, which may cause a mild local allergic reaction through histamine release. This causes local vasodilatation, in contrast to the vasoconstriction seen with EMLA, which may be of value in preparing the skin for venepuncture.

Inhalation

Inhaled drugs may be intended for a local or systemic site of action. The particle size and method of administration are significant factors in determining whether a drug reaches the alveolus and, therefore, the systemic circulation, or whether it only penetrates into the upper airways. Gases and drugs present in droplets of less than 1 micron diameter (which may be generated by an ultrasonic nebulizer) can reach the alveolus and present themselves for systemic absorption. However, a larger droplet or particle size results in drug falling against airway mucosa from the larynx to the bronchioles, so that virtually none reaches the alveolus.

Local Site of Action

The bronchial airways are the intended site of action for inhaled or nebulized bronchodilators. However, drugs given for a local or topical effect may be absorbed to give systemic effects. Chronic use of inhaled steroids may lead to Cushingoid side-effects, while high doses of inhaled b2 agonists (e.g. salbutamol) may lead to tachycardia and hypokalaemia. Nebulized adrenaline, used for upper airway oedema causing stridor, may be absorbed and lead to tachycardia, arrhythmias and hypertension. In addition, when lignocaine is applied locally to

anaesthetize the pharynx before fibreoptic intubation, sufficient quantities may be absorbed to cause systemic toxicity.

Inhaled nitric oxide reaches the alveolus and dilates the pulmonary vasculature. It is absorbed into the pulmonary circulation but its short half-life prevents systemic side-effects.

Systemic Site of Action

The large surface area (70 m2 in an adult) available for absorption provides the potential for a rapid onset of action.

Clearly the ultimate site of action of volatile anaesthetic agents is the central nervous system. Although the precise mechanism of action at a cellular and subcellular level remains to be determined, it is known that the more soluble the inhaled anaesthetic is in lipid, the greater its potency. MAC (minimum alveolar concentration) describes the potency of an anaesthetic agent, with a low MAC implying a high potency. Agents with a high oil:gas solubility are highly potent (and, therefore, have a low MAC). The MeyerOverton hypothesis relates oil:gas solubility to MAC and shows an inverse correlation between the two for a wide range of agents.

The kinetics of the inhaled anaesthetics are covered in greater detail in Chapter 8

Epidural

In anaesthetic practice the epidural route is used to provide analgesia and to augment general anaesthesia. Local anaesthetics, opioids, ketamine and clonidine have all been used for acute pain, while steroids continue to be used for diagnostic and therapeutic indications in patients with chronic pain. When used to treat acute pain, drugs are given via a catheter sited in the epidural space, and may be given as a single bolus, a series of boluses or by infusion.

Local anaesthetics are used widely by infusion to block sensory fibres, but they may also block the large motor fibres supplying the legs. While low concentrations may not be sufficient to block pain, higher concentrations may result in a significant motor block. However, ropivacaine may provide improved sensory motor discrimination so that pain relief is achieved with a minimal motor block. The addition of an opioid (often fentanyl at 2 µg.ml1) to a low concentration of local anaesthetic provides the best combination of analgesia with minimal motor block.

For caesarean section, a denser and more extensive block is required than that used in labour. In addition to an increased dose of local anaesthetic, a further dose of opioid is often given via the epidural catheter. Lignocaine, with a lower pKa than bupivacaine, and therefore a faster onset of action, is often used to 'top up' the block. The onset time may be further reduced by adding sodium bicarbonate, thereby increasing pH, which increases the amount available in the unionized

form. Adrenaline may also be added to the solution to increase the duration of the block, by inducing local vasoconstriction and reducing efflux of local anaesthetic from the epidural space.

Significant amounts of drug may be absorbed from the epidural space into the systemic circulation especially as drugs are often administered for extended periods by this route. Local anaesthetics and opioids are both commonly administered via the epidural route and carry significant morbidity when toxic systemic levels are reached.

Intrathecal

While the amount of drug administered by this route is very small it all reaches the systemic circulation eventually.

Distribution

The process of distribution depends on the factors that influence the passage of drug across the cell membrane, which have been discussed in Chapter 1. These factors include: molecular size, lipid solubility, degree of ionization and protein binding. Drugs fall into three general groups:

• Those confined to the plasmacertain drugs (e.g. dextran 70) are confined to the plasma as they are too large to pass between cells, while other drugs (e.g. warfarin) may be so intensely protein bound that the unbound fraction is tiny, so that the amount available to cross the cell membrane is immeasurably small.

• Those with limited distributionthe non-depolarizing muscle relaxants are polar, poorly lipid-soluble and bulky. Therefore, their distribution is limited to tissues supplied by capillaries with fenestrae (i.e. muscle) that allow their movement out of the plasma.

• Those with extensive distribution. These drugs are invariably highly lipid-soluble. However, some may also be highly protein-bound (e.g. propofol), but due to the dynamic nature of protein binding this does not limit their distribution. In addition, some drugs are sequestered by tissues (amiodarone by fat; iodine by the thyroid; tetracyclines by bone).

Those drugs that are not confined to the plasma are initially distributed to those tissues with the highest blood flow (brain, lung, kidney, thyroid, adrenal) then to those tissues with a lower blood flow (muscle), and finally to those tissues that have a very low blood flow (fat). These tissue groups are less well defined in vivo but they provide a useful model with which to explain observed plasma levels following drug administration.

BloodBrain Barrier (BBB)

The BBB is an anatomical and functional barrier between the circulation and the central nervous system. It consists of a number of apposed cell layers. The capillary endothelium is in intimate contact with a basement membrane, adjacent to which are peripheral processes of the astrocytes. The overlapping tight junctions restrict passive diffusion, and the process of pinocytosis is absent.

Active diffusion is therefore the predominant method of molecular transfer, which in health is tightly controlled. Glucose and hormones, such as insulin, cross by active carrier transport, while only lipid-soluble, low molecular weight drugs can cross by simple diffusion. Inhaled and intravenous anaesthetics have these properties, and therefore cross readily (to cause their anaesthetic effect) whereas the large polar steroid-based muscle relaxants cannot cross and have no central effect. Similarly, due to glycopyrrolate's charge it does not cross the BBB readily, unlike atropine, which may cause confusion or a paradoxical centrally mediated bradycardia.

As well as providing an anatomical barrier, the BBB contains enzymes such as monoamine oxidase. Therefore, monoamines are converted to non-active metabolites by passing through the BBB. Physical disruption of the BBB may lead to central neurotransmitters being released into the systemic circulation and partially explain the marked circulatory disturbance seen with head injury and subarachnoid haemorrhage.

In the healthy subject penicillin penetrates the BBB poorly. However, in meningitis, the nature of the BBB alters as it becomes inflamed, and its permeability to penicillin (and other drugs) increases, allowing it to reach its intended site of action.

Drug Distribution to the Foetus

The placental membrane that separates foetal and maternal blood is initially derived from the apposed placental syncytiotrophoblast and foetal capillaries, which subsequently fuse to form a single membrane. Being phospholipid in nature, the placental membrane is more readily crossed by lipid-soluble than polar molecules. However, it is less selective than the BBB and even molecules with only moderate lipid solubility appear to cross with relative ease and significant quantities may appear in cord (foetal) blood. In contrast to most tissues, the foetus has its own excretory pathways, and the drugs crossing the placenta are generally excreted in the foetal urine, preventing the foetal plasma level reaching significance.

The effects of maternal pharmacology on the foetus may be divided into those effects that occur in pregnancy, especially the early first trimester and the period of organogenesis, and those at birth.

Drugs during Pregnancy

Experimentation with animal models may provide some evidence of safety, although interspecies variation may prevent teratogenicity in animals while resulting in significant teratogenicity in humans. In addition, the effects of a drug's teratogenicity may not be apparent for some years. When taken during pregnancy, stilboestrol predisposes the female offspring to ovarian cancer at puberty. In general, it is preferable either to avoid all drugs throughout pregnancy, or to keep to those treatments with a long history of safety.

There are conditions, however, where the risk of not taking medication outweighs the theoretical or actual risk of teratogenicity. Thus, the danger of an epileptic fit in a known epileptic warrants the continuation of anti-epileptic medication while pregnant, and the presence of an artificial heart valve mandates the continuation of anticoagulation despite the attendant risks.

Drugs at the Time of Birth

Drugs may be administered for analgesia during labour, or as part of an anaesthetic (either regional or general) for caesarean section. The effects of drug therapy are largely predictable from consideration of the basic pharmacological principles. Drugs with a low molecular weight that are lipid soluble diffuse most readily, and large polar molecules diffuse poorly.

Bupivacaine, the local anaesthetic most commonly used for epidural analgesia, crosses the placenta less readily than does lignocaine, due to its higher pKa rendering it more ionized than lignocaine at physiological pH. However, the foetus is relatively acidic with respect to the mother, and if the foetal pH is diminished further due to placental insufficiency, the phenomenon of ion trapping may become significant. The fraction of ionized bupivacaine within the foetus increases as the foetal pH falls, its charge preventing it from leaving the foetal circulation, so that levels rise towards toxicity.

Pethidine is commonly used for analgesia during labour. Its high lipid solubility enables significant amounts to cross the placenta and reach the foetus. Following its metabolism, the less lipid soluble norpethidine accumulates in the foetus, levels peaking about 4 hours after the initial maternal intramuscular dose. Owing to reduced foetal clearance the half-lives of both pethidine and norpethidine are prolonged up to three times.

Thiopentone crosses the placenta rapidly, and experimentally it has been detected in the umbilical vein within 30 seconds of administration to the mother. Serial samples have shown that the peak umbilical artery (and hence foetal) levels occur within 3 minutes of maternal injection. There is no evidence that foetal outcome is affected with an 'injection to delivery' time of up to 20 minutes after injection of a sleep dose of thiopentone to the mother.

The non-depolarizing muscle relaxants are large polar molecules and essentially do not cross the placenta. Therefore, the foetal neuromuscular junction is not affected. Only very small amounts of suxamethonium cross the placenta, though again this usually has little effect. However, if the mother has an inherited enzyme deficiency and cannot metabolize suxamethonium, then maternal levels may remain high and a significant degree of transfer may occur. This may be especially significant if the foetus has also inherited the enzyme defect, in which case there may be a degree of depolarizing blockade at the foetal neuromuscular junction.

Metabolism

While metabolism usually reduces the activity of a drug, the activity may be unaltered or increased (a pro-drug is defined as a drug that has no inherent activity before metabolism, but which is converted by the body to an active moiety). Metabolism may also produce a metabolite with equivalent activity to the parent compound, in which case it produces no net effect.

In general, metabolism produces a more ionized molecule that allows excretion in the bile or urinethe chief routes of drug excretion. There are two phases of metabolism, I and II.

Phase I
(Functionalization or Non-synthetic)

- Oxidation
- Reduction
- Hydrolysis

Most phase I reactions are carried out in the liver by a non-specific enzyme system termed the mixed-function oxidase system which resides in the endoplasmic reticulum. The multitude of enzymes responsible is termed the cytochrome P450 system, after the wavelength (in nm) of their maximal absorption of light, when the reduced state is combined with carbon monoxide. However, the cytochrome P450 system is not unique to the liver. Methoxyflurane is metabolized by CYP2E1 in the kidney, generating a high local concentration of F, which may cause renal failure (cf. sevoflurane metabolism, p92).

The enzymes of the cytochrome P450 system are classified into families and subfamilies by their degree of shared amino acid sequencesfamilies share 40% and subfamilies 55% respectively of the amino acid sequences. In addition, the subfamilies are further divided into isoforms of a particular subfamily. For nomenclature, the families are labelled CYP1, CYP2, etc., the subfamilies CYP1A, CYP1B, etc. and the isoforms CYP1A1, CYP1A2, etc.

However, some drugs rely on different enzymes for their metabolism. The monoamines are metabolized by the mitochondrial enzyme monoamine oxidase. Individual genetic variation, or the presence of exogenous inhibitors of this breakdown pathway, can result in high levels of monoamines in the circulation, with severe cardiovascular effects.

In addition, some processes take place in the plasma. Atracurium breaks down spontaneously in a pH- and temperature-dependent mannerHofmann degradation, and esters are hydrolysed by non-specific esterases.

Phase II
(Conjugation or Synthetic)

- Glucuronidation
- Sulphation
- Acetylation
- Methylation
- Glycination

Although most drugs are initially metabolized by a phase I reaction and then by a phase II reaction, some drugs are modified by phase II reactions only. Phase II reactions increase the water solubility of the metabolite (or drug) to allow excretion into the bile or urine. They occur mainly in the hepatic endoplasmic reticulum but other sites such as the lung may also be involved. This is especially true in the case of acetylation, which also occurs in the lung and spleen.

In liver failure, phase I reactions are generally affected before phase II, so drugs with a predominantly phase II metabolism are less affected.

Genetic Variants and Metabolism

There are inherited differences in enzyme structure that alter the way drugs are metabolized in the body. The abnormal enzymes with the greatest relevance to anaesthesia are plasma cholinesterase and those involved in acetylation.

Suxamethonium is metabolized by hydrolysis in the plasma, a reaction that is catalysed by the relatively non-specific enzyme plasma cholinesterase. Certain individuals have an unusual variant of the enzyme, and metabolize suxamethonium much more slowly. Several autosomal recessive genes have been identified, and these may be distinguished by their various in vitro inhibition by substances such as fluoride and the local anaesthetic cinchocaine. Paralysis by the muscle relaxant may be prolonged in the abnormal populations. This is discussed in greater detail in Chapter 11.

Acetylation is a phase II pathway in the liver. Drugs metabolized by this pathway include hydralazine, procainamide, isoniazid and phenelzine. Different populations have different enzymes that metabolize at a slow and fast rate respectively. The pharmacokinetic profile of these drugs in the different populations is therefore different, and the expected effect of a drug will be different according to the acetylator status of the individual.

Enzyme Inhibition and Induction

Some drugs (Table 2.1) induce the activity of the hepatic microsomal enzymes, increasing both phase I and II reactions. The rate of metabolism of the enzyme-inducing drug as well as other drugs is increased and may lead to reduced plasma levels. Other drugs, especially those with an imidazole structure, inhibit the activity of hepatic microsomal enzymes and may result in increased plasma levels.

Excretion

Elimination refers to the processes of removal of the drug from the plasma and includes distribution and metabolism, while excretion refers to the removal of drug from the body. The chief sites of excretion are in the urine and the bile (and hence the gastrointestinal tract), although traces of drug are also detectable in tears and breast milk. The chief route of excretion of the volatile anaesthetic agents is via the lungs; however, metabolites are detectable in urine, and indeed the metabolites of agents such as methoxyflurane may have a significant effect on renal function.

The relative importance in the route of excretion of a drug depends upon its nature and molecular weight. In general, high molecular weight compounds (> 30 000) are not filtered or secreted by the kidney and are therefore preferentially excreted in the bile.

Table 2.1: Effects of various drugs on hepatic microsomal enzymes.

	Inducing	Inhibiting
Antibiotics	rifampicin	metronidazole, isoniazid, chloramphenicol
Alcohol	chronic abuse	acute use
Inhaled anaesthetics	enflurane, halothane	
Barbiturates	phenobarbitone, thiopentone	
Anti-convulsants	phenytoin, carbamazepine	
Hormones	glucocorticoids	
MAOI		phenelzine, tranylcypromine
H2 antagonists		cimetidine
Others	cigarette smoking	amiodarone

Renal Excretion

Filtration at the Glomerulus

Small, non-protein-bound, poorly lipid soluble (therefore readily water soluble) drugs are excreted into the glomerular ultrafiltrate. It should be remembered that protein binding is a dynamic process between the bound and unbound fraction. As unbound drug is filtered at the glomerulus the equilibrium is altered, until bound drug dissociates from its binding site, to restore the unbound fraction. Therefore, protein binding slows down, but does not prevent glomerular filtration, and moderately bound drugs may be filtered to a significant extent.

Secretion at the Proximal Tubules

This is an active energy-requiring process at the proximal convoluted tubules, and a wide variety of molecules may be excreted into the urine against their concentration gradients by this mechanism. Acidic and basic drugs have different transport systems for their excretion and are capacity-limited for each drug type (i.e. maximal clearance of one acidic drug will result in a reduced clearance of another acidic drug, but not of a basic drug). Drug secretion may also be inhibited, e.g. probenecid blocks the secretion of penicillin.

Diffusion at the Distal Tubules

At the distal tubule, passive diffusion may occur down the concentration gradient. Acidic drugs are preferentially excreted in an alkaline urine as this increases the fraction present in the ionized form, which cannot be reabsorbed. Conversely, basic drugs are preferentially excreted in acidic urine where they are trapped as cations.

Biliary Excretion

High molecular weight compounds, such as the steroid-based muscle relaxants, are excreted in bile. Secretion from the hepatocyte into the biliary canaliculus takes place against a concentration gradient, and is therefore active and energy-requiring, and subject to inhibition and competition for transport. Certain drugs are excreted unchanged in bile (e.g. rifampicin), while others are excreted after conjugation by a phase II reaction (e.g. morphine is excreted as the glucuronide).

Enterohepatic Circulation

Drugs excreted in the bile such as glucuronide conjugates are hydrolysed in the small bowel by glucuronidase-secreting bacteria. The drug is now much more lipid-soluble and is reabsorbed into the portal circulation where it travels to the liver and is reconjugated and excreted in the bile. This process may continue many times. Failure of the oral contraceptive pill while taking broad-spectrum antibiotics has been blamed on a reduced intestinal bacterial flora causing a reduced enterohepatic circulation of oestrogen and progesterone.

Effect of Disease

Renal Disease

In the presence of renal disease, those drugs that are normally excreted via the renal tract may accumulate. This effect will vary according to the degree to which the drug is excreted renallyin the case of a drug whose clearance is entirely renal, a single dose may have a very prolonged effect. Therefore, the clearance of gallamine, a non-depolarizing muscle relaxant, is so renally dependent that if given in the context of renal failure dialysis or haemofiltration is required to reduce the plasma level and hence reverse the pharmacological effect.

If it is deemed necessary to give a renally excreted drug in the presence of renal impairment, a reduction in dose must be made. If the apparent volume of distribution remains the same, the loading dose also remains the same, but the subsequent amount of drug that needs to be given to achieve the same plasma level is less. This is usually reflected in an increased dose interval or reduced dose. However, due to fluid retention the volume of distribution is often increased in renal failure.

Knowledge of a patient's creatinine clearance is very helpful in estimating the dose reduction required for a given degree of renal impairment. As an approximation, the dose, D, required in renal failure is given by:

$$D = \text{Usual dose} \times \frac{\text{Impaired clearance}}{\text{Normal clearance}}$$

Tables contained in the *British National Formulary* give an indication of the appropriate reductions in mild, moderate and severe renal impairment.

Liver Disease

Hepatic impairment has a multifactorial influence on pharmacokinetics. Protein synthesis is decreased (hence decreased plasma protein levels and reduced protein binding). Both phase I and II reactions are affected, and thus the metabolism of drugs into inactive moieties is reduced. In addition, the presence of portocaval shunts means that drugs previously cleared by passage through the liver have direct access to the systemic circulation.

There is no exactly analogous measure of hepatic function to compare with the creatinine clearance that may be measured for the kidney. Liver function tests in common clinical use may be divided into those that measure the synthetic function of the liverthe international normalized ratio (INR) or prothrombin time and albuminand those that measure inflammatory damage of the hepatocyte. Though interrelated, it is possible to have a markedly inflamed liver with high transaminase levels, which retains reasonable synthetic function. In addition,

albumin is a negative acute phase reactant, the level of which is therefore diminished in any acute illness.

Patients with severe liver failure may suffer hepatic encephalopathy as a result of a failure to clear ammonia and other molecules. These patients are very susceptible to the effects of benzodiazepines and opioids, which should therefore be avoided if possible. For patients requiring strong analgesia in the peri-operative period a co-existing coagulopathy will often rule out a regional technique, leaving few other analgesic options other than to titrate intravenously the minimum amount of opioid required, accepting the risk of precipitating encephalopathy.

The Extremes of Age

Neonate and Infant

In the newborn and young, the pharmacokinetic profiles of drugs are different for a number of reasons. These are due to qualitative, as well as quantitative, differences in the neonatal anatomy and physiology.

Fluid Compartments

The volume and nature of the pharmacokinetic compartments is different, with the newborn being relatively overhydrated, and losing volume through diuresis in the hours and days after birth. As well as the absolute proportion of water being higher, the relative amount in the extracellular compartment is increased. The relative sizes of the organs and regional blood flows are also different from the adult.

Distribution

Plasma protein levels and binding are less than the adult. In addition, the pH of foetal blood tends to a lower value, which alters the relative proportions of ionized and unionized drug. Thus, both the composition and acid-base value of the blood affect plasma protein binding.

Metabolism and Excretion

While the neonate is born with several of the enzyme systems functioning as the adult's, the majority of enzymes do not reach maturity for a number of months. Plasma levels of cholinesterase are reduced, and in the liver the activity of the cytochrome P450 family of enzymes is markedly reduced. Newborns have a reduced rate of excretion via the renal tract. The creatinine clearance is less than 10% of the adult rate per unit body weight, with nephron numbers and function not reaching maturity for some months after birth.

Though the implications of many of these effects may be predicted, the precise use of drugs in the newborn has largely been determined clinically, and in general prescription is preferred for those drugs that have been used safely for a number

of years, and in which the necessary dose adjustments have been derived empirically. In addition, there is wide variation between individuals of the same postconceptual age.

Elderly

A number of reasons contribute to differing pharmacokinetics in the elderly. The basic pharmacokinetic parameters change as organ function deteriorates with increasing age. The elderly have a relative reduction in muscle mass, with a consequent increase in the proportion of fat. There is a reduction in the activity of hepatic enzymes with increasing age, leading to a relative decrease in hepatic drug clearance. Creatinine clearance diminishes steadily with age, reducing renal excretion.

As well as the changes of age, the elderly are more likely to have co-existing disease. The implications of this are two-fold. First, the disease process may alter drug handling by the body and, second, the drug treatment of that disease may cause drug interactions.

3
Drug Action

Mechanisms of Drug Action

Drugs may act in a number of ways to exert their effect. These range from the relatively simple actions that depend on the physiochemical properties of a drug to highly specific actions at enzymes and receptors.

Actions Dependent on Chemical Properties

The antacids exert their effect by directly neutralizing gastric acid.

The chelating agents are used to reduce the concentration of certain metallic ions within the body. Dicobalt edetate chelates cyanide ions and may be used in cyanide poisoning or following a potentially toxic dose of sodium nitroprusside. The tetracyclines chelate iron, calcium and magnesium, but in doing so reduce their own absorption.

Non-Specific Membrane Action

Many anaesthetic agents act on the cell membrane in a non-specific manner that is independent of action on any specific receptor. The precise mechanism by which this occurs is still unknown. The close correlation between oil:gas (and, therefore, membrane) solubility and potency implies that increasing the amount of agent dissolved in the membrane increases the anaesthetic effect. However, it remains to be determined whether the action is purely within the lipid bilayer or located to specific molecules contained within the membrane.

The wide range of molecular structures with an anaesthetic effect implies a general rather than a specific mechanism of action. Considering the diversity of structure from nitrous oxide to ketamine and thiopentone, it is clear that a single receptor is unlikely to be the site of action. Until recently it was thought that the general size and shape of the molecule caused a non-specific membrane effect that prevented neural transmission. However, work with stereoisomers of different agents (e.g. isoflurane and ketamine) has shown that one isomer may have a

greater anaesthetic effect than the other. This implies a more specific interaction with a molecule or series of molecules, rather than simply changing a physical property of the lipid bilayer.

Whatever the precise mechanism of action, the net effect is hyperpolarization, which increases the stimulus required to achieve the depolarization threshold and, hence, stabilizes the cell.

Enzymes

Enzymes are biological catalysts, and drug action on enzymes is usually one of inhibition. The action has two effects: the concentration of the substrate normally metabolized by the enzyme is increased, and that of the product of the reaction catalysed is decreased. Angiotensin-converting enzyme (ACE) inhibitors inhibit the conversion of angiotensin I to II, and of bradykinin to various inactive fragments. While reduced levels of angiotensin II are responsible for the therapeutic effects when used in hypertension and heart failure, raised levels of bradykinin may cause an intractable cough.

Enzyme inhibition may be competitive (edrophonium and the ACE inhibitors), non-competitive (neostigmine) or irreversible (organophosphorous compounds and many monoamine oxidase inhibitors).

Receptors

A receptor is a specific molecule to which a ligand binds to exert its effect. A ligand is any substance able to bind to a receptor recognition siteit does not have to cause an effect. Ligands may also bind to more than one receptor and have a different mechanism of action at each (e.g. ionotropic and metabotropic actions of g-aminobutyric acid (GABA) at GABAA and GABAB receptors).

Receptors are generally protein or glycoprotein in nature and may lie in the cell membrane, the cytosol or the cell nucleus. Those in the membrane are generally for ligands that do not readily penetrate the cell, while those in the cytosol and nucleus are for lipid-soluble ligands that can diffuse through the cell wall to their site of action.

Receptors may be grouped into three classes depending on their mechanism of action: (1) altered ion permeability; (2) production of intermediate messengers; and (3) regulation of gene transcription.

1
Altered Ion Permeability:
Ion Channels

Here, ligand binding causes a change in the structure of the membrane protein complex (the ion channel) altering its permeability to ions (ionotropic).

The nicotinic receptor at the neuromuscular junction is bound by acetylcholine causing a rapid increase in Na+ flux through its central ion channel, leading to membrane depolarization.

Benzodiazepines bind to GABA type A receptors, increasing the opening frequency of the chloride channel, which leads to neuronal hyperpolarization. They do not bind directly to the same site as GABA, but to the a subunit of the activated receptor complex to augment chloride ion conductance.

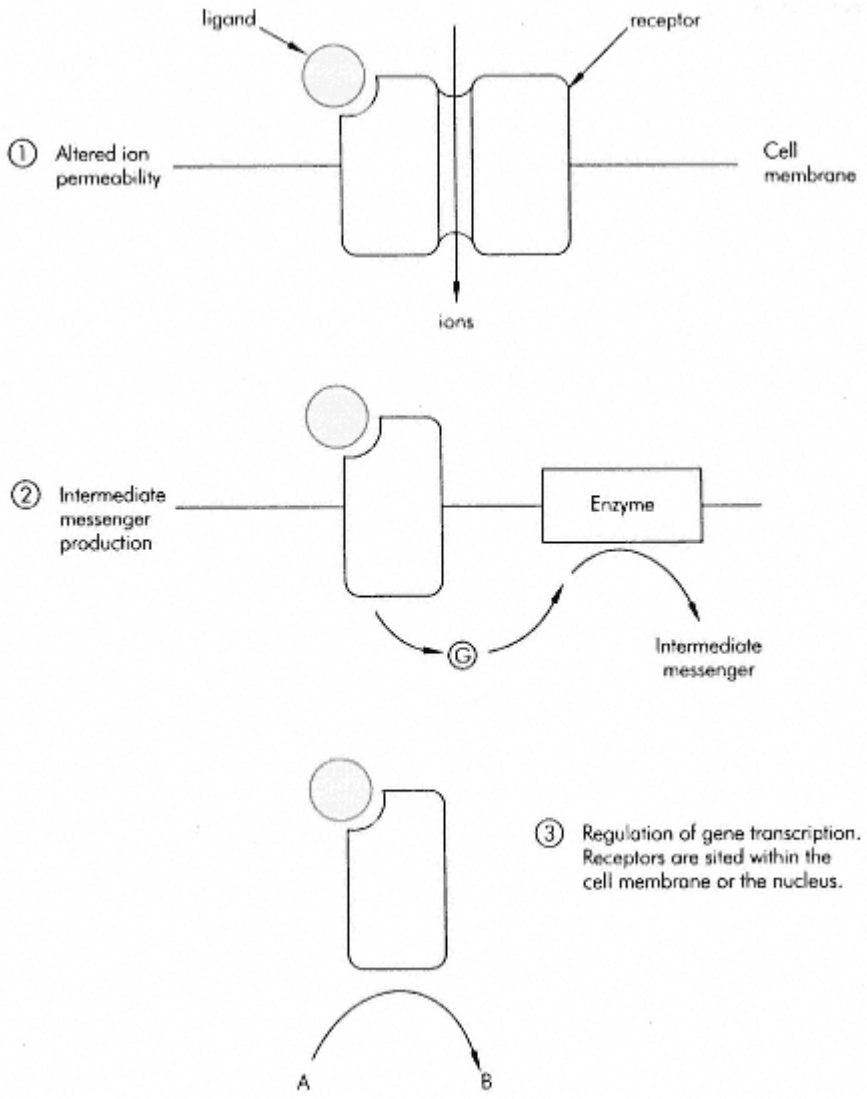


Figure 3.1:
Mechanism of action of the three groups of receptors.

2
Production of Intermediate Messengers:
G Proteins

G proteins are a complex series of proteins that act as universal transducers to effect an intracellular change from an extracellular stimulus. Receptors that act via a G protein and an intermediate messenger are termed metabotropic. As well as transmitting a stimulus across the cell membrane (without the need for effector molecules to cross the cell boundary), the G protein system produces signal amplification, whereby a modest stimulus may have an exaggerated intracellular response. This is because the intermediate messengers may be reused after an initial stimulus, so that the ligand effecting the reaction may have a continued action.

G proteins consist of an a, b and g subunit, and bind GDP and GTP, after which they are named. In the inactive form the a subunit is bound to GDP. On interaction with an active ligandreceptor complex the GDP is exchanged for cGTP, giving a complex of acGTP bg. The acGTP subunit then dissociates from the bg subunit and activates or inhibits an effector protein (adenylate cyclase, guanylate cyclase or phospholipase Csee below) (Figure 3.2).

The a subunit itself acts as a GTPase enzyme, splitting the cGTP attached to it to regenerate an inactive a-GDP subunit. This then reforms the entire inactive molecule by recombination with another bg subunit.

The a subunit of the G proteins shows marked variability, with at least 17 molecular variants arranged into three main classes. The variety of different subunits is responsible for various G proteins having different initiating ligands, even though they may share the same intermediate messengers.

Adenylate cyclase catalyses the formation of cAMP, which acts as a final common pathway for a number of extracellular stimuli. G proteins are termed Gs if they stimulate and Gi if they inhibit the production of cAMP. The cAMP so formed acts by stimulating protein kinase A, which has two regulatory (R) and two catalytic (C) units. cAMP binds to the R unit, revealing the active C unit, which is responsible for the biochemical effect, and it may cause either protein synthesis, gene activation or changes in ionic permeability.

cAMP formed under the regulation of the G proteins is broken down by the action of the phosphodiesterases (PDEs). The PDEs are a family of five isoenzymes, of which PDE III is the most important. PDE inhibitors prevent the breakdown of cAMP so that intracellular levels rise.

Therefore, in the heart, positive inotropy is possible by either increasing cAMP levels (with a b agonist or a non-adrenergic inotrope such as glucagon), or by reducing the breakdown of cAMP (with a PDE III inhibitor such as milrinone).

Guanylate cyclase catalyses the formation of cGMP, which has a limited role as an intermediate messenger. Some hormones and neurotransmitters mediate their

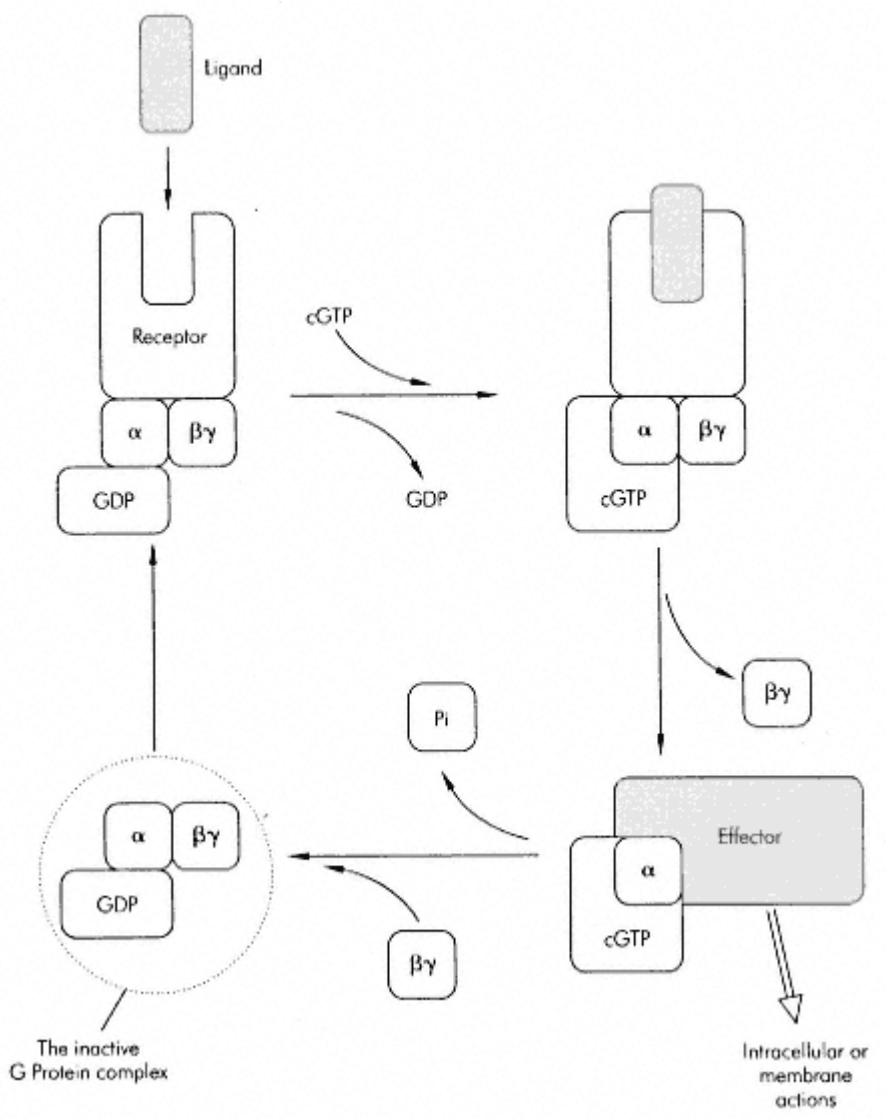


Figure 3.2:
G protein cycle (see text for details).

actions via cGMP. The G proteins have an almost identical function in its generation compared with cAMP.

Atrial natriuretic peptide and nitric oxide exert their effects by increasing the levels of intracellular cGMP by stimulating guanylate cyclase.

Phospholipase C is also under the control of the G proteins, but the protein class is termed Gq. Activation of the Gq proteins by ligand binding to a receptor to form

an active ligandreceptor unit promotes the action of phospholipase C. This breaks down phosphatidylinositol 4,5-bisphosphate (PIP2) to form inositol triphosphate (IP3) and diacylglycerol (DAG).

The two molecules thus formed each have specific actionsIP3 causes calcium release in the endoplasmic reticulum, and DAG causes activation of protein kinase C, with a variety of biochemical effects specific to the nature of the cell in question. Increased calcium levels act as a trigger to many intracellular events, including enzyme action and hyperpolarization. Again, the common messenger will cause specific effects according to the nature of the receiving cellular subcomponent.

a1 Adrenoreceptors and angiotensin I receptors exert their effects by activation of the Gq proteins.

3
Regulation of Gene Transcription

Membrane tyrosine kinase. Certain drugs and natural compounds including insulin and growth factor act through the tyrosine kinase system, which is contained within the cell membrane, resulting in a wide range of physiological effects.

The insulin receptor consists of two a and two b subunits, and spans the cell membrane. When a ligand binds to the a subunits, the tyrosine residues on its b subunits are phosphorylated, which greatly increases their tyrosine kinase activity. This phosphorylation is then responsible for generating the intracellular action.

In general, the effects of the tyrosine kinase receptors are to control the events of cell growth and differentiation by the regulation of gene transcription.

Cytosol and DNA in the cell nucleus. Steroids and thyroid hormones act to alter the expression of DNA and RNA. They indirectly alter the production of cellular proteins by modifying the transcription process, and hence, the formation of cell proteins. The effects are therefore necessarily slow. There are discrete proteins in the cytosol that bind the steroid molecule, and it is the steroidreceptor complex which is then transferred to the cell nucleus to its site of action at the DNA.

Dynamics of Drug-Receptor Binding

The binding of a ligand (L) to its receptor (R) is represented by the equation:

$$L + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} LR$$

This reaction is reversible. The law of mass action states that the rate of a reaction is proportional to the concentrations of the reacting components. Thus, the velocity of the forward reaction is given by:

$V_1 = k_1.[L].[R],$

where k1 is the rate constant for the forward reaction (brackets indicate concentration).

The velocity of the reverse reaction is given by:

$V_2 = k_2.[LR],$

where k2 is the rate constant for the reverse reaction.

At equilibrium, the reaction occurs with the same rate in both directions (V1 = V2), and the equilibrium constant Ka is given by the equation:

$$K_a = \frac{[LR]}{[L].[R]} = \frac{k_1}{k_2}$$

Ka is termed the affinity constant and is a reflection of the strength of binding between the ligand and receptor. Its reciprocal, KD, is the equilibrium dissociation constant.

Types of Drug-Receptor Interaction

The two properties of a drug that determine the nature of its pharmacological effect are affinity and activity.

- Affinity refers to how well or avidly a drug binds to its receptorin the analogy of the lock and key, this is how well the key fits the lock.

- Activity (often termed intrinsic activity or efficacy) refers to the magnitude of effect the drug has once bound.

It is important to distinguish these properties. A drug may have a high affinity, but minimal activity, and thus binding will produce no pharmacological response. If such a drug prevents the binding of a more active ligand, this ligand will be unable to exert its effectand the drug is demonstrating receptor antagonism. Therefore:

- an agonist has receptor affinity and intrinsic activity

- an antagonist has receptor affinity but no intrinsic activity.

Receptor Agonism

Full Agonists

Full agonists are drugs able to generate a maximal response from a receptor. Not only do they have a high affinity for the receptor, but also they have a high intrinsic activity.

Partial Agonists

If a drug has only moderate intrinsic activity, such that it occupies receptors, but produces a submaximal effect compared with the full agonist, it is termed a partial agonist. The distinguishing feature of partial agonists is that they fail to achieve a maximal effect even in very high dose (i.e. with full receptor occupancy) (Figure 3.3).

Inverse Agonists

It is possible for a drug to bind and exert an effect opposite to that of the endogenous agonist. Such a drug is termed an inverse agonist and, similarly to a full or partial agonist, it may have high or moderate affinity. The difference between an inverse agonist and a competitive antagonist is importantan inverse agonist will exert its own (opposite) pharmacological effect to an agonist, whereas a competitive antagonist has no direct effect of its own, but acts by preventing the agonist from exerting its action.

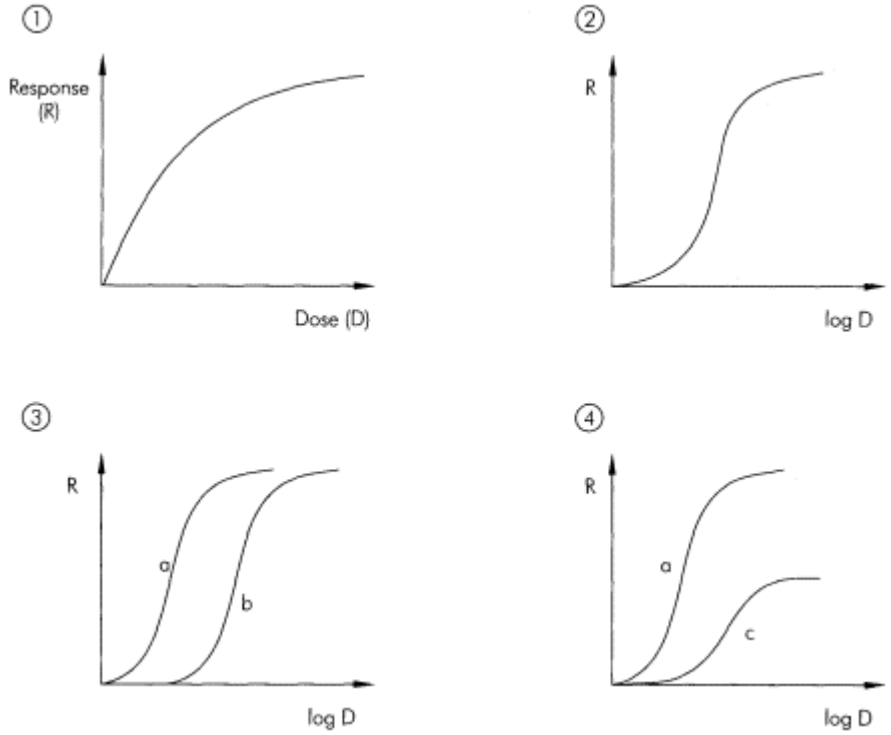


Figure 3.3:
Doseresponse curves. (1) Normal agonist doseresponse curve. (2) This curve is plotted using a log scale for dose and produces the classical sigmoid shape. (3) Here there is a parallel shift of the curve to the right (b), which may represent the response of a full agonist in the presence of a competitive antagonist or an irreversible antagonist at low dose. Curve 'b' may also represent a full agonist of lower potency. (4) Curve 'c' represents a partial agonist that is unable to elicit a maximal response despite high drug concentration. It may also represent the response of a full agonist in the presence of an irreversible antagonist at high concentration.

Receptor Antagonism

Antagonists exhibit affinity but no intrinsic activity. Their binding may be either reversible or irreversible.

Reversible

Here, the effect of the antagonist may be overcome by increasing the concentration of the agonistthe two molecules are competing for the same receptor and the relative amounts of each (combined with receptor affinity) determine the ratios of receptor occupation. Examples include the non-depolarizing muscle relaxants, b-blockers and anti-muscarinics.

Irreversible

Here, increasing agonist concentration will not change the receptor occupancy ratio, and the effect, therefore, cannot be overcome by increased agonist dose. Phenoxybenzamine irreversibly binds to and antagonizes the effects of catecholamines at a adrenoreceptors.

pA2

pA2 is used to describe the efficacy of competitive reversible antagonism of receptor blockade. The term refers to the negative logarithm in base 10 of the concentration of antagonist required, such that a doubling of agonist concentration is needed to achieve the same pharmacological effect.

Thus, if a concentration of 105 mmol antagonist added to a solution requires a doubling of agonist concentration to achieve the same effect, then the pA2 = log 105, which is 5.

Antagonism of Neuromuscular Transmission

The neuromuscular junction contains acetylcholine (ACh) receptors, which when occupied by ACh cause depolarization of the motor end plate. However, only one-quarter of these receptors needs to be occupied to produce a maximal pharmacological effect. Occupancy of only a small proportion of the receptors ensures that a small quantity of ACh produces a maximal response. As a result there are 'spare receptors'. If a high occupancy was required to generate a response, a relative over-supply of ACh would be required. This would be wasteful in terms of the energy required for ACh synthesis, and the time taken to achieve full occupancy would delay the rate of propagation of the signal.

In general, at the neuromuscular junction, weaker antagonists have a more rapid onset of action. This is because they are given in a higher dose for the same maximal effect so that more molecules are available to occupy receptors, and the receptor occupancy required for full effect is achieved more rapidly. Rocuronium, a non-depolarizing muscle relaxant, has only one-fifth of the potency of

vecuronium, and therefore is given at five times the dose for the same effect. The relative flooding of the receptors means that the threshold receptor occupancy is achieved more rapidly, with a clear clinical benefit.

Tachyphylaxis, Desensitization and Tolerance

Repeated doses of a drug may lead to a change in the pharmacological response, which may be increased or decreased for the same dose.

Tachyphylaxis

Tachyphylaxis is defined as a rapid decrease in response to a repeated dose, over a short period. The commonest mechanism is the decrease of stores of a transmitter before resynthesis can take place. An example is the diminishing response to repeated doses of ephedrine, an indirect acting sympathomimetic amine caused by the depletion of noradrenaline.

Desensitization

Desensitization refers to a chronic loss of response over a longer period and may be due to a structural change in receptor morphology, or an absolute loss of receptor numbers. The term is often used synonymously with tachyphylaxis.

Tolerance

Tolerance refers to the phenomenon whereby larger doses are required to produce the same pharmacological effect, such as occurs in chronic opioid use or abuse. This reflects an altered sensitivity of the receptors of the central nervous system to opioidsthe mechanism may be reduction of receptor density, reduction of receptor affinity or a reduction in absolute numbers. Tolerance occurs if nitrates are given for prolonged periods as the sulphydryl groups on vascular smooth muscle become depleted. A drug holiday of a few hours overnight when the need for vasodilatation is likely to be at its lowest allows replenishment of the sulphydryl groups and restoration of the pharmacological effect.

4
Drug Interaction

Interactions occur when one drug modifies the action of another. This interaction may either increase or decrease the second drug's action, with wanted or unwanted effects.

Drug interaction can occur at many levels, whether by direct chemical interaction either outside or within the body, or by biochemical antagonism. This may be at the level of an individual cell, at the level of a specific tissue or at the level of the whole organism. The chance of a significant interaction increases markedly with the number of drugs usedin addition, the effects of any interaction are often exaggerated in the presence of disease or coexisting morbidity.

About one in six inpatient drug charts contain a significant drug interaction, one-third of which are potentially serious. An uncomplicated general anaesthetic for a relatively routine case may use ten or more different agents, and the possibility of interaction with the patient's medication should also be borne in mind.

Pharmaceutical

These interactions occur because of a chemical or physical incompatibility between the preparations being used. Sodium bicarbonate and calcium will precipitate out of solution as calcium carbonate when given in the same giving set. However, one agent may inactivate another without such an overt indication to the observer; insulin may be denatured if prepared in solutions of dextrose and may, therefore, lose its pharmacological effect. Drugs may also react with the giving set or syringe itself and, therefore, need a special delivery vehicle, such as a glass syringe (e.g. paraldehyde). Glyceryl trinitrate is absorbed by polyvinyl chloride; therefore, special polyethylene administration sets are preferred.

Pharmacokinetic

Absorption

In the case of drugs given orally, this occurs either as a result of one drug binding another in the lumen of the gastrointestinal tract or by altering the function of the

gastrointestinal tract as a whole. Charcoal can adsorb drugs in the stomach, preventing absorption through the gastrointestinal tract (the charcoal is activated by steam to cause fissuring, thereby greatly increasing the surface area for adsorption). Metoclopramide when given as an adjunct for the treatment of migraine reduces gastrointestinal stasis, which is a feature of the disease, and speeds the absorption of co-administered analgesics. This is an example of a favourable interaction.

Distribution

Drugs that decrease cardiac output (such as b-blockers) reduce the flow of blood carrying absorbed drug to its site of action. The predominant factor influencing the time to onset of fasciculation following the administration of suxamethonium is cardiac output, which may be reduced by the prior administration of b-blockers. In addition, drugs that alter cardiac output may have a differential effect on regional blood flow and may cause a relatively greater reduction in hepatic blood flow.

Chelating agents are used therapeutically in both the treatments of overdose, and of iron overload in conditions such as haemochromatosis. The act of chelation combines the drug with the toxic element and prevents tissue damage. Sodium calcium edetate chelates the heavy metal lead and is used as a slow intravenous infusion in the treatment of lead poisoning. Dicobalt edetate chelates cyanide ions and is used in the treatment of cyanide poisoning, which may occur following the prolonged infusion of sodium nitroprusside.

Competition for binding sites to plasma proteins may cause drug interaction. The commonest example seen in practice is the administration of a highly protein-bound drug to a patient on warfarinthe displacement of the warfarin leads to an increased free level in the plasma and, therefore, an increased pharmacological effect. Common culprits in this regard include erythromycin and amiodarone, the commencement of which can cause a previously stable patient to become grossly coagulopathic.

Metabolism

Enzyme induction will increase the metabolism of drugs metabolised by the cytochrome P450 family. Therefore, enzyme induction by alcohol will increase the rate of hepatically metabolized drugs. Conversely, drugs may inhibit enzyme activity, leading to a decrease in metabolism and an increase in plasma levels (see Table 2.1).

Excretion

Sodium bicarbonate by rendering the urine more alkaline will enhance the excretion of acids such as aspirin. Thus, aspirin overdose has been treated with infusions

of fluid to produce a diuresis, together with sodium bicarbonate, to alkalinize the urine and to promote its renal excretion.

Pharmacodynamic

Drugs may interact at the same site, at nearby sites or at anatomically distant sites, so reflecting a different range of mechanisms.

The actions of non-depolarizing muscle relaxants (NDMRs) are additive as long as drugs of a similar group are used. By an unknown mechanism, steroidal NDMRs and benzylisoquinolinium NDMRs are synergistic.

The actions of enoximone and adrenaline to produce positive inotropy, though having the common effect of increasing cAMP levels, are at different sites on the cardiac muscle cell. Captopril and b-blockers act additively not only to lower blood pressure, but also at different sites via the renin-angiotensin system and via adrenoreceptors respectively.

Diuretics through their action on the levels of potassium may cause digoxin toxicity in a patient who was previously stable.

Summation

Summation refers to the action of the two drugs being additive, with each drug having an independent action in the absence of the other. Therefore, the administration of midazolam as well as propofol at the induction of anaesthesia reduces the amount of propofol necessary for the same anaesthetic effect.

Potentiation

Potentiation is the action of the drugs in combination being greater than that of the first alone, with the second drug having no action of its own if given independently. For example, probenecid reduces the renal excretion of penicillin, such that the effect of a dose of penicillin is enhanced without itself having antibiotic activity.

Synergism

The combined action of the drugs is more than that which would be expected from purely an additive effect. Often, this is because the drugs are having a similar end effect through different mechanisms. Antibiotics are often used in combination and are sometimes formulated in the same preparation.

The nature of interactions between different agents may be studied by use of an isobologram (Gk *isos*, equal; *bolus*, effect). An isobologram describes the interaction between two different drugs plotted on the x- and y-axes. For a given intensity of

effect a line may be drawn giving the relative contributions of the two drugs to that effect. A straight line describes a purely additive effect. Where the line is convex a greater amount of drug is needed to achieve a similar intensity of effect and, therefore, it describes an inhibitory interaction. In contrast, a concave line describes a similar intensity of effect but with reduced amounts of drugs, whose interaction is therefore synergistic (Figure 4.1).

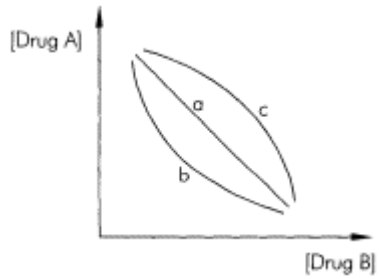


Figure 4.1:
Isobolograms with lines of equal activity:
a, additive; b, synergistic; c, inhibitory.

5
Isomerism

Isomerism is the phenomenon by which molecules with the same atomic formulae have different structural compositionsthe constituent atoms of the molecule are the same, but they are arranged in a different configuration. There are two broad classes of isomerism:

- structural isomerism
- stereoisomerism

Structural Isomerism

Molecules that are structural isomers have identical chemical constituents, but the bonds between the atoms are arranged differently. Depending on the degree of similarity between the structures there may be a range of similarities of pharmacological action, from identical to markedly different. Isoflurane and enflurane both behave as volatile anaesthetic agents with a broadly similar action. Prednisolone and aldosterone, again structural isomers, show a more significant difference in activity, with the former having glucocorticoid and mineralocorticoid actions, and the latter behaving primarily as a mineralocorticoid. Isoprenaline and methoxamine, again structural isomers, have different cardiovascular effects, with methoxamine acting predominantly via a adrenoreceptors and isoprenaline acting via b adrenoreceptors. Dihydrocodeine and dobutamine are also structural isomers. However, the molecular structure and pharmacological effects are so diverse that it is little more than coincidence that the corresponding chemical constituents happen to be identical (Figure 5.1).

Tautomerism

Tautomerism refers to the dynamic interchange between two forms of a molecular structure, often precipitated by a change in the physical environment. For example, midazolam, which is ionized in solution at pH 4, changes into a seven-membered unionized ring structure at physiological pH 7.4, rendering it lipid-soluble and making it, therefore, rapidly acting (see Figure 17.1). Similarly,

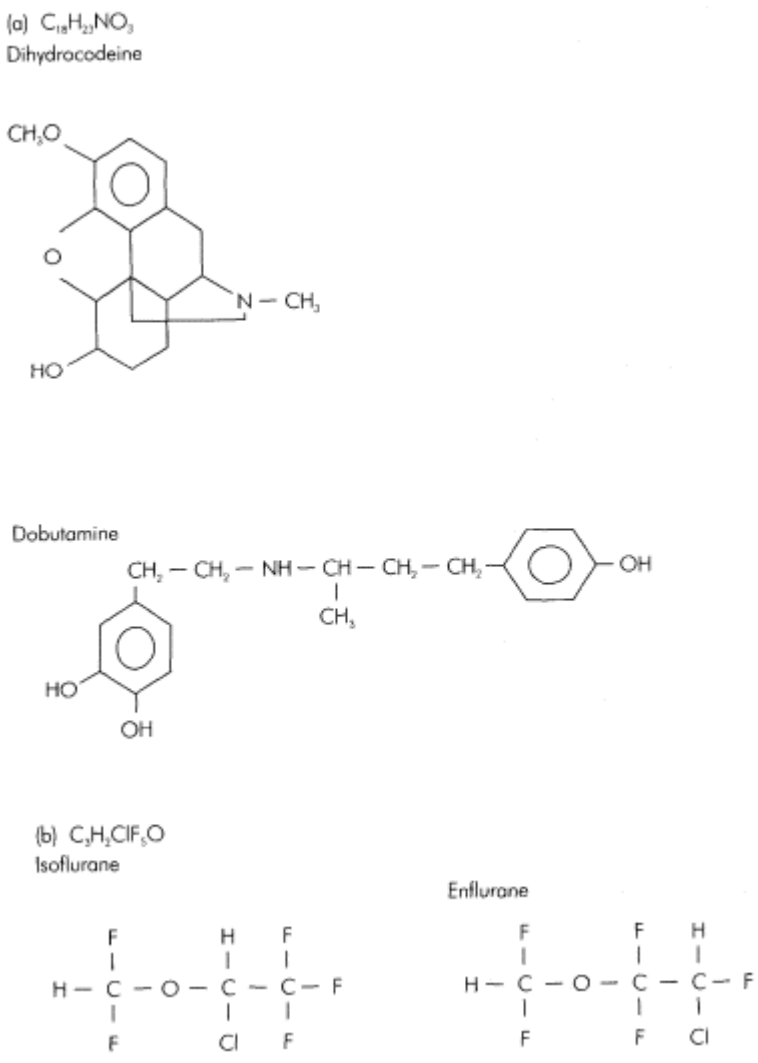


Figure 5.1:
Structural isomers; (a) C18H23NO3; (b) C3H2ClF5O.

morphine may undergo a keto-enol transformation, altering the structure between two forms of approximately equal stability.

Stereoisomerism

Stereoisomers have both the same chemical constituents and bond structure as each other but a different three-dimensional configuration. The three-dimensional configuration can be different for the same bond structure in the presence of a

- single chiral centre or
- more than one chiral centre or a carbon-carbon double bond

Enantiomers

A Single Chiral Centre

A chiral atom is one bound to four different atoms or combination of atoms. The different configurations so formed may be classified according to the molecular weights of the substituent groups on the four bonds of the chiral atom, and whether the molecular weights ascend in a clockwise or anticlockwise fashion when the molecule is arranged with the largest group facing away from the viewer. This leads to an R and S (from the Latin *rectus* and *sinister*) pair of structures, which are mirror images of each other. This may be referred to as 'handedness', and the structures are referred to as enantiomers. It is the preferred nomenclature as the relationship between the substituent groups is fixed. Both carbon and nitrogen may form chiral centres (Figure 5.2).

In addition, the different stereoisomers have a different effect on polarized light and will rotate a transmitted beam of polarized light in different directions, either to the right or to the left. This leads to the classification of isomers into () or laevo-rotatory (left-rotating), or (+) or dextro-rotatory (right-rotating) forms. However, there is no link between the R and S classification and the laevo and dextro classification, and an S structure may be laevo or dextro-rotatory to polarized light.

The nature of the different three-dimensional structures alters the effect of the compound at a molecular level. However, if a molecule has a general action, caused by dissolving in a membrane, there may be no difference between the properties of the stereoisomers, but if the action is on a receptor there may be a marked difference between different isomers.

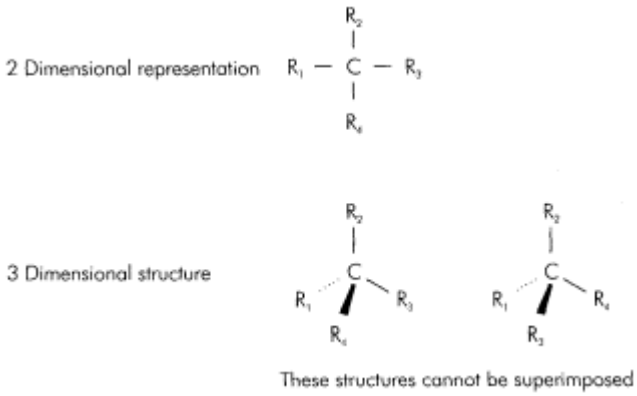


Figure 5.2:
Chiral centres.

Diastereoisomers

Where pairs of stereoisomers do not demonstrate 'handedness', i.e. they are not enantiomers, the term diastereoisomers is used. This occurs where more than one chiral centre is present and where a carbon-carbon double bond exists.

More than one chiral centre. If a molecule contains more than one (e.g. 'n') chiral atoms, then 2n combinations are possible. Though the maximal number of possible isomers is 2n, some molecules exhibit internal symmetry, such that some of the possible configurations duplicate themselves. Atracurium has four chiral atoms (two carbon atoms, two quaternary nitrogen atoms) and, therefore, in theory 16 enantiomers, but in reality it has only ten distinct three-dimensional structures. Pairs of these stereoisomers may not be mirror images and cannot be classified as enantiomers.

Carbon-carbon double bond. Geometric isomerism exists when a molecule has a double bond linking two carbon atoms with dissimilar attachments, with resistance to rotation around the double bond. For one double bond, a range of possible configurations exists depending upon whether the primary attachments are on the same or opposite aspects of the bond. Thus the configuration may be cis-cis, trans-trans or cis-trans in nature. Again, pairs of these stereoisomers may not be mirror images and cannot be classified as enantiomers.

Anaesthetic agents (local and inhaled) may not contain stereoisomers, either because the molecule is symmetrical so that only one form exists (e.g. propofol), or because only one of the variety of possible structures is administered (e.g. ropivacaine, given as a single isomer preparation). The majority of naturally synthesized agents (e.g. d-tubocurare) are produced as single isomers, but become racemates in the purification process (e.g. atropine).

Racemic Mixtures

These are mixtures of different stereoisomers in equal proportions. Examples include the volatile agents and bupivacaine. While the mixture may contain equal amounts of the two isomers, the contribution to activity, both pharmacodynamic and pharmacokinetic, may be very different and, indeed, one may be responsible for undesirable toxicity or side-effects.

Enantiopure Preparations

There may be benefit in specifically selecting the more desirable moiety from a racemic mixture and administering it as a single isomer preparation (i.e. enantiopure). R-ropivacaine has a more toxic profile than S-ropivacaine so that it is presented in an enantiopure formS-ropivacaine. The enantiopure S-bupivacaine is also currently undergoing trials.

6
Mathematics and Pharmacokinetics

Pharmacokinetics is the study of the way in which the body handles administered drugs. The use of mathematical models allows prediction of the fate of a drug once administered, and the effects of changing the dose and interval between doses. Mathematical models may be used to program computers to deliver variable rate infusions to achieve a certain predicted plasma level.

It should be remembered that the models upon which pharmacokinetics are based make a number of assumptions. The less sophisticated models make more general assumptions and the real life situation may not be as simple as the models lead us to believe. Therefore, although convenient and useful to group various tissues together as 'well perfused' or 'poorly perfused', this remains only an approximation of the physiological state in practice.

Mathematics

The Exponential Function

Many of the pharmacokinetic processes rely on the exponential functionthe function of first-order kinetics. This process is common throughout the natural world, and describes the rate of change (dC/dt) of a variable (C) as being proportional to the level of that variable (Figure 6.1):

$$dC/dt \propto C$$

or

$$dC/dt = K.C.$$

Bacterial replication is an example of an exponential increase. However, where there is an exponential decrease (e.g. drug elimination) a negative sign is present to reflect the direction of change.

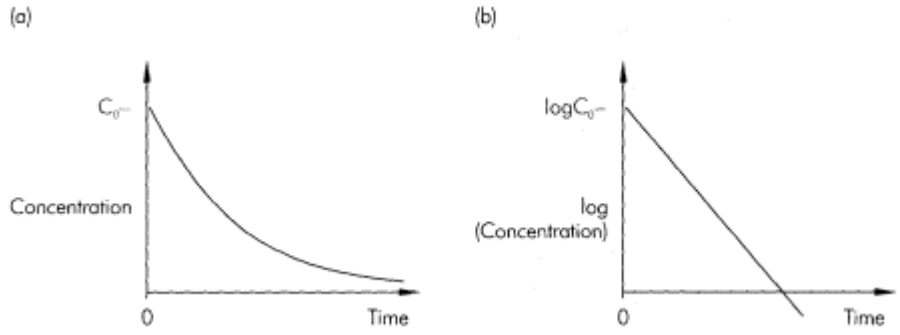


Figure 6.1:
(a) Exponential decrease in plasma concentration of drug against time after a bolus dose of a drug displaying single-compartment kinetics. (b) A logarithmic scale used on the y-axis produces a straight line (C0 is the plasma concentration at time, t = 0).

$dC/dt = -K.C.$

Integration of this equation gives

$C = C_0 . e^{-Kt}.$

Taking natural logarithms (ln) of each side:

$\ln C = \ln C_0 . e^{-Kt}.$

Therefore,

$\ln C = \ln C_0 + \ln e^{-Kt}$ as $\ln (AB) = \ln A + \ln B$

and

$\ln C = \ln C_0 - Kt$ as $\ln e^{-Kt} = -Kt$

so that

$\ln (C/C_0) = -Kt.$

K is termed the rate constant and represents the proportional change in C in unit time. It is important to note that a rate constant has the dimensions of time1 and, therefore, the units of, for example, min1. Therefore, the rate constant for the transfer of propofol from compartments 1 to 2 in its pharmacodynamic model is 0.114 min1, not 0.114 mg.min1.

The reciprocal of the rate constant is termed the time constant, and has the dimensions of time and the units of, for example, minutes. It is given the symbol t, or

tau, and represents the time required for C to fall to 1/e of its former value. This would be the time taken for the initial concentration to reach zero if the initial rate of decline was to continue. 'e' is the mathematical constant forming the base of natural logarithms, and is about 2.72. 1/e is, therefore, about 0.368. Thus, one time constant is the time taken for C to fall to 0.368 or 37% of its former value. The time constant t is necessarily longer than the half-life (see below) (Figure 6.2).

Asymptotes

Theoretically, an exponential process approaches its steady-state without ever actually reaching it. The line that the function approaches is termed the asymptote (Figure 6.3). In practice, after five half-lives, the process is 50 + 25 + 12.5 + 6.25 + 3.125 = 96.875% complete, and five half-lives is by convention taken to represent the time taken to achieve steady-state.

Alternatively, three time constants represent the time assumed to be needed to achieve steady-state.

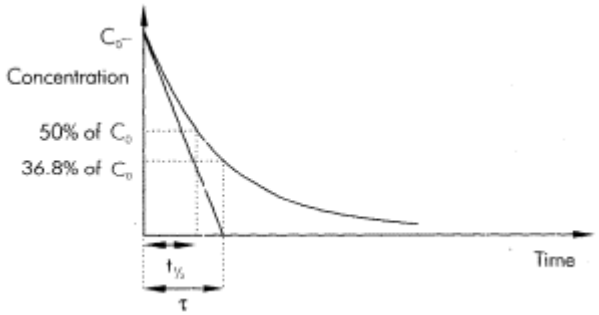


Figure 6.2:
Comparison between t and half-life ($t_{½}$).

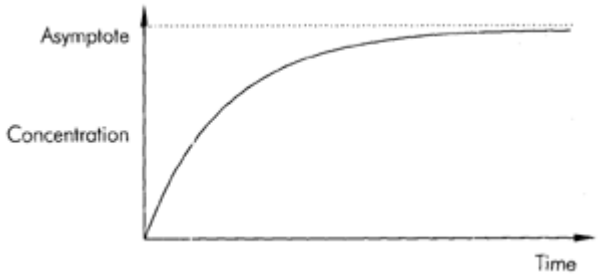


Figure 6.3:
Asymptote.

Pharmacokinetics

The Single-Compartment Model

The single-compartment model assumes that the injected drug is confined to one compartment, where it exerts its pharmacological effect, and from which it is eliminated in an exponential fashion. The concepts discussed below are most easily understood in relation to the single-compartment model.

Volume of Distribution, Clearance and Half-Life

These concepts are extremely useful in the modelling of pharmacokinetics, and are intrinsically linked. Volume of distribution (Vd) represents an apparent volume that reflects the distribution of the drug throughout the body. Clearance (Cl) reflects the rate of elimination of drug from the plasma. Terminal half-life is the time taken for the plasma level to fall by 50% during the terminal phase of decline, and it depends on the volume of distribution and clearance.

- *Volume of distribution (Vd)*

Vd is defined as the apparent volume that a drug would occupy if it were present in that volume at the same concentration as is actually found in plasma. In other words, it is a constant (for a given drug) that relates the plasma concentration to the dose required to achieve that concentration. It has the units of volume (e.g. litres) but is often indexed and expressed as litres.kg1 bodyweight.

Vd depends on tissue protein binding, the partition coefficients of the drug, which reflect how avidly the drug is sequestered in the different tissues of the body, and on the regional blood flow to these tissues. Vd is the initial dose divided by the plasma concentration:

Vd = dose/plasma concentration.

Where a drug is bound in the tissues, such that its plasma concentration is very low, Vd will be correspondingly high, as if the drug had been injected into a large volume of homogenous tissue. Propofol and fentanyl are subject to significant tissue binding and have large Vds of 4.0 l.kg1. Propofol is also 98% plasma protein-bound, but the dynamic nature of the binding allows unbound drug to pass into tissues.

It is important to realise that the Vd is theoretical and can exceed total body volume. Vd can suggest the sites of distribution of a drug, whether confined to the plasma or spread equally throughout total body water.

- *Clearance (Cl)*

Cl is defined as the volume of plasma from which the drug is completely removed per unit timethe usual units are ml.min1.

Cl reflects elimination of the drug from the plasma, which may be via the liver (the main site for drug metabolism), the kidneys (often excreting unchanged drug) and distribution into tissues.

• *Terminal half-life*

In the single-compartment model, Vd and Cl are linked by the terminal half-life. This is the time taken for the plasma concentration to fall to 50% of its initial value during the exponential process of drug elimination (Figure 6.2).

The half-life and, therefore, the time for elimination may be increased for two reasons:

• If the renal clearance is low, then less drug is eliminated in each passage through the kidneys, and elimination is prolonged.

• If Vd is high, then the plasma contains a lower concentration of drug. As only that drug which is present in the plasma is available for excretion, again elimination is prolonged.

The rate constant, Cl and Vd are in fact interrelated. If K represents the rate constant for the exponential process of elimination, then

$$K = Cl/Vd.$$

If Cl is low or Vd is high, then the rate constant is small and elimination proceeds slowly.

As the time constant, t, is given by:

$$\tau = 1/K$$

then

$$\tau = Vd/Cl.$$

In a simple one-compartment model, knowledge of Vd of a drug allows prediction of the loading dose.

• *Loading dose, infusion rate and dose interval*

The loading dose (LD) for a required plasma concentration Cp is given by:

$$LD = Vd.C_p.$$

The rate of drug elimination is given by multiplying clearance (i.e. ml.min1 cleared of drug) with plasma concentration (i.e. mg drug in each ml cleared):

$$Rate_{el} = Cl.C_p.$$

If given as an infusion, in steady-state (i.e. with unchanging plasma concentration), the rate of drug influx (Ratein) must equal the rate of drug elimination:

$Rate_{in} = Rate_{el}$

$Rate_{in} = Cl.C_p$.

Often, it is permissible for the plasma concentration of a drug to lie within a range, rather than attaining a precise value. This allows the drug to be given as repeated boluses, achieving a peak plasma level which then declines to the minimal level, at which point a further dose is given. After an initial loading dose, a maximal plasma concentration will be reached. After one half-life, the concentration will have fallen to half of this value. If this concentration is acceptable as the minimum plasma concentration, then the dose frequency is equal to one elimination half-life (Figure 6.4).

In reality, however, few processes can be modelled accurately this way. The commonest example of importance in anaesthesia is when the action of a drug is terminated by distribution rather than excretion. Thus, although the elimination half-life of thiopentone is some hours, its pharmacological action is terminated within minutes by distribution to vessel-rich tissues and then to fat. This requires the more sophisticated two- and three-compartment models to predict behaviour.

Multi-Compartment Models

Multi-compartment models address the problems of the different distributions to different tissues within the body, and the different blood flow rates to these tissues, by assuming that some tissues can be viewed as compartments, with equal pharmacological properties. Convenient labels include 'vessel rich' and 'vessel poor' compartments. The number of theoretical compartments that may be included in the model is limitless, but more than three compartments become experimentally indistinguishable (Figure 6.5).

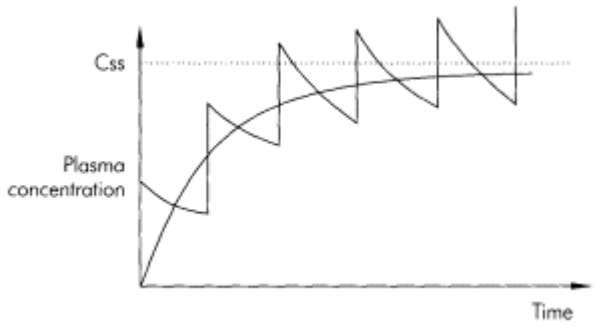


Figure 6.4:
Accumulation of a drug with intermittent boluses given at its half-life compared with infusion of the same total dose. The steady-state concentration (within 95%) is reached after five half-lives.

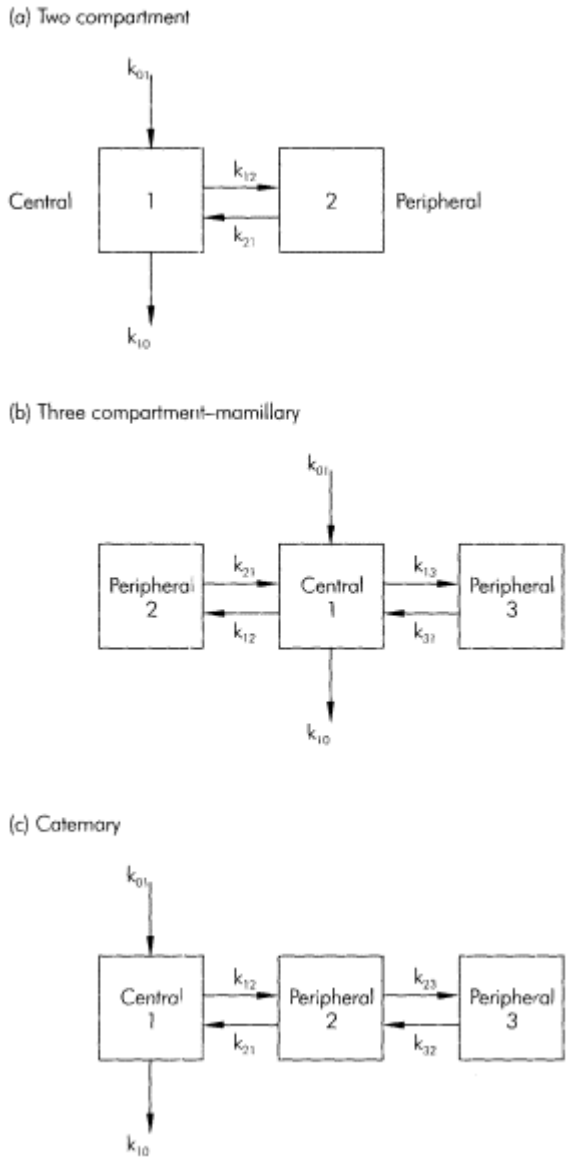


Figure 6.5:
Multi-compartment models:
(a) two compartments;
(b) three compartmentsmamillary;
(c) three compartmentscaternary.

Two Compartments

By convention, the 'compartment' outside the patient is given the suffix '0', the plasma or central compartment the suffix '1', and the second or peripheral compartment the suffix '2'.

Transfer between compartments is assumed to occur in an exponential fashion according to the differences in concentration ratio and, therefore, has a rate constant. Thus, k01 represents the rate constant for the transfer of drug from the outside to the plasma, and k12 the rate constant for the transfer from central to peripheral compartment.

A rapid initial decline in concentration after bolus injection results from distribution into the peripheral compartment. There is then a slower decline due to terminal elimination. Plotting the plasma values on a graph shows these two processes.

Extrapolating the two components of the curve allows dissection of the two exponential processes of distribution and elimination, the rate constants of which are given the suffixes a and b respectively (Figure 6.6).

Since the gradient of an exponential plot is K, where K is the rate constant, the gradients of the two lines are thus a and b, and the curve of plasma concentration (Cp) at time t has the equation:

$$C_p = A.e^{-\alpha t} + B.e^{-\beta t},$$

where A and B are constants. The intercepts on the y-axis (i.e. when t = 0) give A and B respectively.

The above equation gives the two rate constants a and b, and the reciprocals of these rate constants give the time constants t-a and t-b. Multiplying by 0.693 converts a time constant to a half-life, and this gives the half-lives t1/2a and t1/2b respectively. These represent the half-lives of the initial distribution and the longer elimination processes of a two-compartment model.

In real terms, the central and peripheral compartments do not correspond to an actual anatomical or physiological tissue. Thus, the central compartment is often larger than just the plasma volume, comprising also the water of the well perfused tissues of the body.

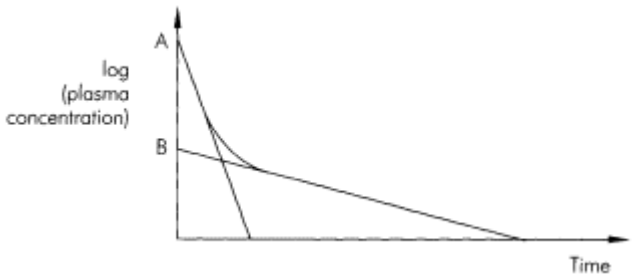


Figure 6.6:
Bi-exponential decline.

Three Compartments

Describing drug pharmacokinetics as three or more compartments leads to increasingly sophisticated models. Again, each compartment has an influx and efflux subject to a pair of exponential processes. Two different arrangements of the compartments are possible.

The most commonly used, and that which reflects the actual physiological situation in the majority of cases, is the mamillary model (Figure 6.5b). The equation for the plasma concentration (Cp) is now given by:

$$C_p = A.e^{-\alpha t} + B.e^{-\beta t} + G.e^{-\gamma t}.$$

B and b are reserved for the elimination half-life, and G and g refer to the kinetics of the additional compartment.

The model consists of a central compartment into which a drug is infused, and from which excretion can occur, with two peripheral compartments with which drug can be exchanged. These may typically represent well-perfused and poorly perfused tissues respectively, with the central compartment representing plasma. This is a reasonable model for the majority of anaesthetic agents, where drug reaches the plasma (via a variety of routes) and is distributed to muscle and fat.

Again, it is important to recognize that the compartments do not necessarily represent a discrete anatomical or physiological tissuerather they represent a variety of discrete tissues whose broadly shared pharmacological profile enables them to be treated as homogenous for the simplicity of mathematical modelling.

The alternative three-compartment model is the caternary model (Figure 6.5c), in which access to the third compartment is only possible via transit through the second. This model is generally used for more unusual or specific pharmacological modelling, and is not as useful as the mamillary model for the majority of processes encountered in anaesthesia and intensive care.

Context Sensitive Half-Times and Conductance Ratios

The elimination half-life is a characteristic often cited in comparisons of different drugs, but this may have little relevance to the situation in vivo if the behaviour is more complicated than predicted by a simple one-compartment model. In a multicompartment model, distribution between different compartments may have a more significant effect on the termination of pharmacological action than terminal elimination.

The process of distribution is relevant in both directionsinitially there is transfer from the central compartment into the 'fast' and 'slow' peripheral compartments, at a rapid and slower rate respectively. (The 'fast' compartment may be

considered as the highly perfused compartment, while the 'slow' compartment may be considered as the poorly perfused compartment described in a three-compartment modelsee below.) On cessation of the infusion into the central compartment, the drug is then transferred back (redistributed) in the reverse direction, which may produce a continued pharmacological effect.

Conductance Ratios

The relative contributions of elimination and distribution in the reduction of the central compartment concentration will be different for different drugs. The term 'conductance ratio' has been proposed to describe the ratio of these rates. The conductance ratio of the fast compartment, Cfast, is given by:

$$C_{fast} = k_{12}/k_{10},$$

where k12 is the rate constant for transfer into the fast compartment, and k10 is the elimination rate constant.

The ratio, therefore, describes the relative importance of distribution and excretion in the termination of a drug's action. If the conductance ratio is high, then after cessation of a steady-state infusion redistribution will play a significant part in maintaining the central compartment concentration. If the conductance ratio is low, then the peripheral compartments release drug gradually over a prolonged period, and the drug thus released is rapidly excreted or metabolized. The concentration, therefore, falls rapidly and is maintained at a very low, and usually insignificant, plasma level as the peripheral compartments slowly become cleared.

Context-Sensitive Half-Times

Knowledge of the elimination half-life alone cannot be used to determine a drug's time-course, as the contributions of elimination and redistribution will both vary between different drugs. In addition, the relative contributions will vary even for the same drug according to the relative loading of the peripheral fast and slow compartments. If a drug has been given as a single bolus, there will be little peripheral loading and the central compartment will be depleted through excretion and by distribution into the peripheral compartments. However, at the end of a steady-state infusion, the peripheral compartments will now return the previously distributed drug to the central compartment and act to maintain, rather than diminish, the central concentration. The term 'context-sensitive half-time' has been introduced, with the term 'context' referring to the duration of infusion.

Context-sensitive half-time is defined as the time for the plasma concentration to decline by half, after the termination of an infusion designed to maintain a constant plasma concentration.

The context-sensitive half-times may differ markedly from the elimination half-lives, and are in general a more useful indicator of a drug's behaviour in the clinical

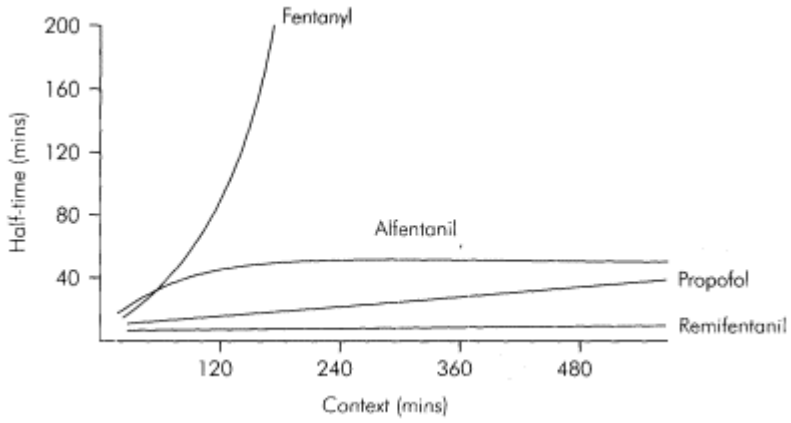


Figure 6.7:
Various context-sensitive half-times.

setting. However, the terms and the values for different intravenous agents are not as yet in widespread use (Figure 6.7).

Remifentanil and Context-Sensitive Half-Time

In contrast to most agents used in anaesthesia, remifentanil has a relatively constant context-sensitive half-time. Remifentanil is a fentanyl derivative that is a pure μ agonist, with an ester linkage, which is rapidly broken down by non-specific tissue and plasma esterases. The metabolites have minimal pharmacodynamic action. The context-sensitive half-time of remifentanil is about 3 minutes, and this is relatively constant over a wide range of contexts (infusion duration). Therefore a patient may be maintained on a remifentanil infusion for an almost arbitrarily long period, without accumulation and without the effects of distribution seen with other opioids. On cessation of the infusion the relatively constant context-sensitive half-time means that the pharmacodynamic effect will rapidly disappear.

The advantage of this pharmacokinetic profile is that a patient may be given remifentanil to cover surgery or to provide sedation and analgesia, with rapid cessation of the effect when this is no longer required. The potential disadvantage is that the cessation of effect is so rapid that if there is still a painful stimulus the patient will be left without analgesia. This must then be supplanted, either by use of a regional technique or by the administration of a longer acting opioid.

Non-Linear Kinetics

Most drugs are handled by the body according to first-order kinetics. This means that plasma levels are governed by the exponential function, and the rate of change is proportional to the amount present. The term 'first-order' reflects thisthe rate

of change of X is proportional to X (i.e. X1, and not X2, X3, etc.). Pharmacological processes are usually first-order as there is a relative excess of enzyme or receptor available compared with the amount of substrate, and the amount of enzyme is, therefore, not rate-limiting.

Some processes, however, obey zero-order kineticsthey are proportional to X0, i.e. 1, where the rate of change is a constant, and is not dependent upon the amount present. This is also termed saturation kinetics and reflects the saturation of receptors or enzymes at a molecular level.

An example of this is the metabolism of ethanol, which proceeds at a relatively constant rate, independently of the amount ingested. This is because the rate-limiting step of its metabolism by the enzyme alcohol dehydrogenase is the presence of another cofactor for the reaction, which is present only in finite quantities.

Certain processes obey first-order kinetics at low dose, but zero order at higher (though still clinical) doses. Thus, the metabolism of phenytoin becomes saturable within the normal range, and the metabolism of thiopentone becomes saturated when used for burst suppression in status epilepticus.

There are two important implications of a process obeying zero-order kinetics, either wholly or at some point in the dose range.

First, towards the upper limit of the normal range, a small increase in dose may cause a large increase in the plasma level. Toxicity may, therefore, be experienced after a modest dose increase. Checking the plasma levels may help prevent this.

Second, the process will never reach a steady-state if the rate of drug delivery exceeds the rate of drug excretion. The plasma level will continue to rise inexorably without a plateau until ingestion stops or complications intervene (Figure 6.8).

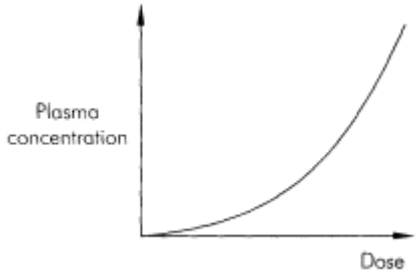


Figure 6.8:
Non-linear (zero-order) kinetics. Plasma concentration is not proportional to the dose as the rate of elimination is constant.

Applied Pharmacokinetics

Propofol

The intravenous anaesthetic propofol has been increasingly used in the latter 1980s and 1990s, and many of its properties approximate to that of the ideal anaesthetic agent. It can be used both for induction and maintenance of anaesthesia, and it has become accepted as the anaesthetic agent of choice in daycase surgery due to its favourable 'wake up' profile. Though it is possible to use propofol without knowledge of its pharmacokinetic properties, even a basic knowledge of its behaviour in the body makes its use more interesting, as it demonstrates many of the fundamental pharmacological principles.

Structure

Propofol is a sterically hindered substituted phenol. The term 'sterically hindered' meaning that the potentially active phenolicOH is shielded by the electron clouds surrounding the attached isopropyl ((CH3)2CH-) groups. It is thus relatively stable, with metabolism eventually being by glucuronidation of the phenol side-chain. None of the metabolites is pharmacologically active.

Pharmacokinetics

The usual induction dose of propofol is 1.52.5 mg.kg1, and this produces rapid loss of consciousness as the lipid tissue of the central nervous system (CNS) takes up the highly lipophilic drug. Over the next few minutes propofol then distributes to peripheral tissues and the concentration in the CNS falls, such that in the absence of further doses or another anaesthetic agent the patient will wake up. Its distribution half-life is 12 minutes (with distribution to the lipid tissues) and is the reason for the rapid fall in plasma levels and its short duration of action. The elimination half-life is much longer (512 hours), but following a single intravenous dose it accounts for the fall in plasma level below that which is required for anaesthesia. Propofol is extensively bound to plasma proteins (97% bound to albumin).

The dose of 1.52.5 mg.kg1 is in fact a relative overdose, but it allows a rapidly injected bolus to induce anaesthesia before true equilibration has occurred. Propofol causes peripheral vasodilatation, possibly through nitric oxide release in a similar manner to nitrates, so that when used in the elderly or hypovolaemic patient it may cause profound hypotension. This may be avoided by giving the drug slowly (or even by infusion to allow the effector compartment levels to build up over a few minutes). In addition, a small bolus dose may be given before the main induction dose. This also starts to preload the effector compartment, so that induction is smoother.

Context-Sensitive Half-Time

The principles of the context-sensitive half-time are discussed above. Half-time refers to the time taken for the plasma level to fall to 50% of the value during

infusion, while context refers to the duration of the infusion. When propofol is used by infusion it steadily loads the peripheral compartments. The longer the duration of the infusion, the more peripheral compartment loading will occur. Therefore, following a prolonged infusion, there will be more propofol to redistribute from the peripheral compartments back into the central compartment, which will tend to maintain the plasma concentration and duration of action. In practice, the longer the duration of the infusion, the longer the time required before plasma levels fall to below that required for anaesthesia. During stimulating and prolonged surgery wake-up times may be as long as 1 hour following total intravenous anaesthesia using propofol.

Anaesthetic Regimes

Propofol may be used to induce and maintain anaesthesia. When used for the maintenance of anaesthesia it may be used as a sole agent or in combination with other anaesthetics and as repeated boluses or by infusion.

If given by boluses, various regimes may be used. A regime of an initial dose of 2.5 mg.kg1 followed by repeated bolus doses of 1 mg.kg1 at 6 minute intervals results in a plasma concentration alternating between about 2.5 and 7.5 µg.ml1. The repeated bolus technique is useful for shorter cases of a few minutes' duration.

Alternatively, an infusion may be used, which is more convenient for longer cases. After an initial loading dose an infusion is started. Experimentally, an infusion of diminishing rate has been shown to give the best approximation to a constant plasma level. This is predictable from consideration of the kineticsas the second and third compartments become loaded by the ongoing infusion they approach steady-state, and the final infusion rate drops to a level matching its excretion.

The Bristol Model

A group from the Sir Humphry Davy Department of Anaesthesia in Bristol published in 1988 a widely known and quoted model of propofol pharmacokinetics. The study used a computer algorithm based on a three-compartment model to design a simple infusion scheme for the manual infusion of propofol to achieve a desired target plasma concentration. The aim was to achieve a target blood concentration of 3 µg.ml1 within 2 minutes and to maintain this level for the duration of surgery.

The study design was as follows:

- ASA 1 or 2 patients presenting for superficial body surgery
- premedication with temazepam 2030 mg, 90 min before surgery
- fentanyl 3 µg.kg1 2 min before the injection of propofol
- propofol 1 mg.kg1 over 20 s

- propofol 10 mg.kg1.h1 for 10 min
- propofol 8 mg.kg1.h1 for 10 min
- propofol 6 mg.kg1.h1 thereafter
- vecuroniun 0.1 mg.kg1 and tracheal intubation
- ventilation with 67% nitrous oxide in oxygen

Results in practice showed an overall mean blood propofol concentration of 3.67 µg.ml1, which was maintained over the subsequent 8090 minutes.

It is important to note the figures for the induction dose of propofol used, and that opioid, nitrous oxide and vecuronium provided balanced anaesthesia. If a loading dose of 2 mg.kg1 of propofol is used, as is common practice, then the 'additional' 1 mg.kg1 is equal to the amount of drug given above a maintenance rate of 6 mg.kg1 h1 by the higher infusion rates of the first 20 minutes. If a loading dose of 2 mg.kg1 of propofol is then followed by a 1086 regime, the propofol concentrations are likely to be higher than predicted, with the attendant cardiovascular effects.

In addition, it is important to realise that the Bristol infusion regime is not a recipe for giving total intravenous anaesthesia; rather, it is an infusion scheme for giving propofol, which it. is hoped will give a blood propofol concentration of 34 µg.ml1. This level may be sufficient, too high or too low, and the infusion regime may need adjusting, either by giving boluses of propofol or by reducing or stopping the infusion altogether to allow the blood level of propofol to fall.

Total Intravenous Anaesthesia (TIVA) and Target-Controlled Infusion (TCI)

Historically, inhalational anaesthesia has moved through the stages of:

- bolus/elimination (with intermittent chloroform drops onto a mask)
- continuous administration (using a vaporizer to deliver a continuous supply of agent)
- estimate of target concentration (with end-tidal agent monitoring)

Intravenous anaesthesia can be considered similarly, but there is no equivalent 'point-of-care' measure of the target concentration; rather the effects of the drug are monitored.

TCI is a relatively new technique that uses a microprocessor-controlled infusion pump that has been programmed with a pharmacological model of the kinetics of propofol. If the patient's weight is entered into the pump, it will infuse propofol at varying rates to give a predicted blood level.

At induction, a bolus is delivered at 1200 ml.h1, giving, for example, a 20 ml bolus over 60 seconds. The infusion is then continued at a diminishing rate as calculated to match the exponential transfer and uptake of drug to different compartments. If a higher predicted blood level is required, for example to cover a highly stimulating point of surgery, then a top-up bolus can be delivered until the theoretical desired level is reached. Similarly, if a lower level is required, the infusion is stopped to allow an exponential fall to the new level, at which point the infusion automatically restarts at a lower rate.

The target blood concentrations are titrated to clinical effect. In the adult the target concentration ranges from 4 to 8 µg.ml1. In the unpremedicated patient an initial target of 6 µg.ml1 can be used, whereas in the premedicated patient an initial target of 4 µg.ml1 may be more appropriate.

Again, it is important to realise that the TCI pump is merely predicting a particular blood level, and that this may not reflect the in vivo level according to the patient's individual pharmacokinetics. In addition, this level may or may not be appropriate for the stage of surgery. While a convenient aid to the anaesthetist, therefore, the infusion must still be adjusted to effect, just as the vaporizer setting may be adjusted during surgery.

The 'decrement time' is a calculated value to give the predicted time for the plasma level to fall to a new value, 1.2 µg.ml1 by default. However, reaching a plasma concentration of 1.2 µg.ml1 does not guarantee that the patient will wake up. Therefore, the decrement time should not be thought of as an 'awakening time', as the latter will be altered by other factors (opioids, benzodiazepines and variable propofol pharmacokinetics).

TIVA and TCI in Practice

Delivering anaesthesia by the inhalational route to a spontaneously breathing patient has an inherent feedback that provides some degree of autoregulation of the depth of anaesthesia. If the patient is too deep, the minute volume falls and delivery of the inhaled anaesthetic is reduced. Conversely, if the patient is too light, the amount of drug delivered is increased, the action tending to deepen the plane of anaesthesia. Although these effects obviously cannot be relied upon entirely, they offer a degree of protection against the possibility of awareness.

With TIVA and TCI (and inhalational anaesthesia in a paralysed patient) this feedback does not exist, and discontinuation of the infusion will result in the patient waking up. The technique if not used carefully will, therefore, result in a higher incidence of awareness. Various measures may be taken to reduce this:

- The infusion should be either via a dedicated intravenous cannula or by a dedicated lumen of a multi-lumen central line, and it should be in view at all times so that a disconnection may be noticed.

- The use of midazolam in a small dose (2 mg) as an adjunct to anaesthesia reduces the incidence of awareness.

- Using oxygen in nitrous oxide rather than air to give an additional analgesic and anaesthetic effect (not strictly TIVA).

The pumps used for TCI infusions have two duplicate sets of circuitry to calculate the infusion rate and predicted effector site levels. If the two independent calculations do not agree, the pump will register this to the anaesthetist.

As always, however, the pump and effector site concentration prediction remain but a guide to the anaesthetist.

SECTION 2
CORE DRUGS IN ANAESTHETIC PRACTICE

< previous page page_65 next page >

7
Intravenous Anaesthetics

Intravenous anaesthetics have been defined as agents that will induce loss of consciousness in one armbrain circulation time.

The introduction of barbiturates in the 1930s was a significant advance in anaesthesia. Their rapid onset and relatively short duration of action made them different from previously used agents. Hexobarbitone was introduced first, followed by thiopentone and subsequently methohexitone. Phencyclidine (angel dust) was withdrawn due to serious psychotomimetic reactions, but the chemically related compound ketamine is still used. The imidazole ester, etomidate, is useful due to its cardiovascular stability but side-effects limit its use. The phenolic derivative propofol has become popular in recent years because of its ready-to-use formulation and favourable recovery profile. Steroidal compounds have also been used, however poor solubility (pregnalolone) together with an association with anaphylactic reactions (due to cremophor ELused to solubalize the steroid althesin) has lead to their demise.

The Ideal Intravenous Anaesthetic Agent

Were an ideal intravenous anaesthetic agent to exist, it should have the following properties:

- rapid onset (mainly unionized at physiological pH)
- high lipid solubility
- rapid recovery, no accumulation during prolonged infusion
- analgesic at sub-anaesthetic concentrations
- minimal cardiovascular and respiratory depression
- no emetic effects
- no pain on injection

- no excitation or emergence phenomena
- no interaction with other agents
- safe following inadvertent intra-arterial injection
- no toxic effects
- no histamine release
- no hypersensitivity reactions
- water-soluble formulation
- long shelf-life at room temperature

The currently used agents are discussed below under the following headings:

- Barbiturates (thiopentone, methohexitone)
- Non-barbiturates (propofol, ketamine, etomidate)

Barbiturates

All barbiturates are derived from barbituric acid, which is the condensation product of urea and malonic acid (Figure 7.1). When oxygen is exchanged for sulphur at the C2 position, oxybarbiturates become thiobarbiturates.

Barbiturates are not readily soluble in water at neutral pH. Their solubility depends on transformation from the keto to the enol form (tautomerism), which occurs readily in alkaline solutions. In general, thiobarbiturates are very lipid-soluble, highly protein-bound and completely metabolized in the liver. In contrast, the oxybarbiturates are less lipid-soluble, less protein-bound and some are excreted almost entirely unchanged in the urine (Table 7.1).

Mechanism of Action

Barbiturates increase the duration (in contrast to benzodiazepines which increase the frequency) of g-aminobutyric acid (GABA)-dependent Cl channel opening in the central nervous system. Increased Cl conductance leads to hyperpolarization and neuronal inhibition. GABAA and GABAB subtypes exist centrally, but thiobarbiturates appear to potentiate only the b subunit within GABAA. Thiobarbiturates also effect Na+ and K+ channels centrally.

Thiopentone

Thiopentone is the sulphur analogue of the oxybarbiturate pentobarbitone.

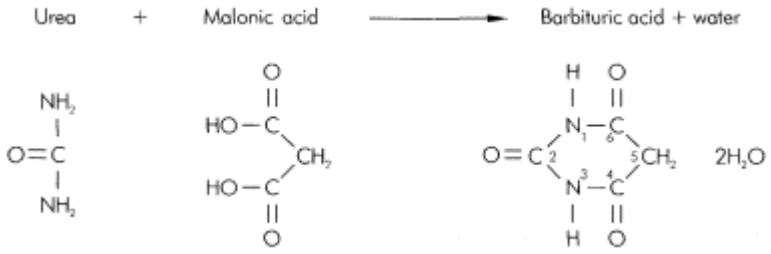


Figure 7.1:
Formation of barbituric acid.

Table 7.1: Lipid solubility and protein binding of a few barbiturates.

	Type	Lipid solubility	Protein binding (%)
Thiopentone	Thio	+ + + + +	80
Pentobarbitone	Oxy	+ + +	40
Phenobarbitone	Oxy	+	10

Presentation

Thiopentone is formulated as the sodium salt and presented as a pale yellow powder.

Sodium thiopentone is a weak acid (pKa 7.6) and forms an alkaline solution when dissolved in water. The undissociated acid is extremely insoluble so two measures are taken to prevent its formation (Figure 7.2).

• Sodium carbonate (6% by weight) is added because it produces OH, thereby preventing accumulation of H+ and formation of the undissociated acid

• It is stored under nitrogen in place of air in a further attempt to prevent acidification of the solution by atmospheric CO2.

The 2.5% solution is stable for many days and should be bacteriostatic due to its pH of 10.5.

Uses

Apart from induction of anaesthesia (37 mg.kg1 intravenously) thiopentone is occasionally used in status epilepticus. It produces an isoelectric EEG when given by continuous infusion confirming maximal reduction of cerebral oxygen requirements. Inotropic support may be required to maintain adequate cerebral perfusion at these doses. It has previously been used rectally, although it has a slow onset via this route.

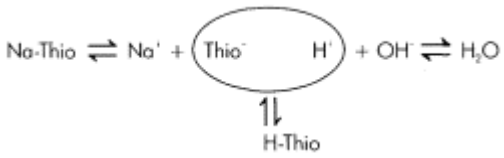


Figure 7.2:
The free acid (H-Thio) is insoluble and would normally precipitate out of solution. To avoid its formation Na-Thio is stored under N2 rather than air, and sodium carbonate is used to increase pH.

Effects

• Cardiovascularthere is a dose-dependent reduction in cardiac output, stroke volume and systemic vascular resistance that may provoke a compensatory tachycardia. These effects are more common in patients that are hypovolaemic, acidotic and have reduced protein binding.

• Respiratoryrespiratory depression is dose-dependent. It may produce a degree of laryngospasm and bronchospasm.

• Central nervous systema single dose will rapidly induce general anaesthesia with a duration of about 5 to 10 minutes. There is a reduction in cerebral oxygen consumption, blood flow, blood volume and cerebrospinal fluid pressure. When used in very low doses it is antanalgesic.

• Renalurine output may fall not only as a result of increased anti-diuretic hormone release secondary to central nervous system depression, but also as a result of a reduced cardiac output.

• Severe anaphylactic reactionsthese are seen in approximately 1 in 20 000 administrations of thiopentone.

• Porphyriait may precipitate an acute porphyric crisis and is therefore absolutely contraindicated in patients with porphyria. The following drugs may also precipitate an acute porphyric crisis:

- other barbiturates
- etomidate
- enflurane
- halothane
- cocaine
- lignocaine and prilocaine (bupivacaine safe)
- clonidine
- metoclopramide
- hyoscine
- diclofenac
- ranitidine

Kinetics

At pH 7.4 only 12% of administered thiopentone is immediately available in the non-protein-bound and unionized form (Figure 7.3). Free drug is 60% unionized. Despite this it has a rapid onset due to its high lipid solubility and the large cardiac output that the brain receives. In addition, a dynamic equilibrium exists between protein-bound and free drug. Critically ill patients tend to be acidotic and have reduced plasma protein-binding, resulting in a greater fraction of drug in the unionized form and fewer plasma protein-binding sites, so that significantly less thiopentone is required to induce anaesthesia. Non-steroidal anti-inflammatory drugs may also reduce available protein binding sites and increase the fraction of free drug.

Rapid emergence from a single bolus dose is due to rapid initial distribution into tissues, not metabolism. A tri-exponential decline is seen representing distribution to well-perfused regions (brain, liver) followed by muscle and skin. The final decline is due to hepatic oxidation mainly to inactive metabolites (although pentobarbitone is also a metabolite). When given as an infusion its metabolism may become linear (zero-order) due to saturation of hepatic enzymes. The hepatic mixed-function oxidase system (cytochrome P450) is induced after a single dose.

Intra-Arterial Injection

Intra-arterial injection causes severe pain due to arterial spasm in the affected limb. As it is not diluted by collateral venous blood in the normal way, its limited solubility at physiological pH causes precipitation of thiopentone acid crystals. These are in effect wedged into vessels of decreasing diameter. Treatment should begin immediately and may include intra-arterial injection of papaverine or procaine, analgesia, sympathetic block of the limb and anticoagulation.

Peri-vascular injection is painful and may cause serious tissue necrosis if large doses extravasate.

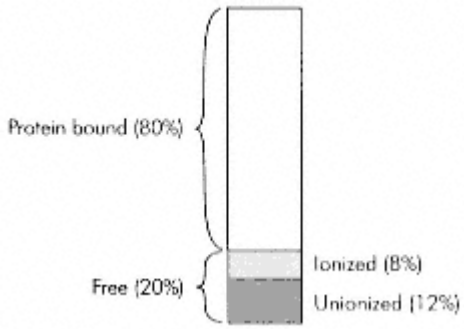


Figure 7.3:
Thiopentone in plasma. Only 12% is immediately available as non-protein-bound and unionized drug.

Methohexitone

Methohexitone is a methylated oxybarbiturate.

Presentation

Methohexitone is produced as the sodium salt with sodium carbonate (6% by weight) and is readily soluble in water to form an alkaline solution (pH 11.0). It has a pKa = 7.9 so that 75% of unbound drug is unionized at pH 7.4. However, 60% of an administered dose is protein-bound. There are four optically active isomers but the preparation used clinically is a racemic mixture of a-D and a-L methohexitone.

Uses

Methohexitone is used as a 1% solution at 12 mg.kg1 for the induction of anaesthesia where excitatory phenomena are of little concern (notably for ECT).

Effects

Methohexitone has a similar pharmacological profile to thiopentone, producing rapid loss of consciousness, rapid emergence due to distribution and exerts similar effects on the cardiovascular and hepatic systems. It may also precipitate a porphyric crisis.

Differences from Thiopentone

Methohexitone may cause an excitatory phase before loss of consciousness, with muscle twitching, increased tone and hiccup. It may precipitate convulsions in those with a history of epilepsy and its use in this setting remains controversial. Recovery is more rapid after methohexitone due to a higher hepatic clearance. When injected intra-arterially or subcutaneously there are fewer vascular complications and there is less tissue damage. This is probably due to the lower concentrations used. Methohexitone is associated with a greater incidence of hypersensitivity reactions although these do not appear to be as severe. Its main metabolite hydroxymethohexitone has only limited hypnotic activity (Table 7.2).

Non-Barbiturates

Propofol

Presentation

This phenolic derivative (2,6 diisopropylphenol) is highly lipid-soluble and is presented as a lipid-water emulsion (containing soya bean oil and purified egg phosphatide) due to poor solubility in water. It is a weak organic acid with a pKa = 11 so that it is almost entirely unionized at pH 7.4.

Table 7.2: Pharmacokinetics of some intravenous anaesthetics.

	Dose (mg.kg1)	Volume of distribution (l.kg1)	Clearance (ml.kg1. min1)	Elimination half-life (h)	Protein binding (%)	Metabolites
Thiopentone	37	2.5	3.5	615	80	active
Methohexitone	1.01.5	2.0	11	35	60	minimal activity
Propofol	12	4.0	3060	512	98	inactive
Ketamine	12	3.0	17	2	25	active
Etomidate	0.3	3.0	1020	14	75	inactive

Uses

Propofol is used for the induction and maintenance of general anaesthesia and for sedation of ventilated patients in intensive care. At a dose of 12 mg.kg1, loss of consciousness is rapid.

Mechanism of Action

This is unclear but is thought to be due to a reduction in Na+ channel opening times. It does not appear to affect the b subunit on the GABAA receptor in a manner similar to the thiobarbiturates.

Effects

• Cardiovascularthe systemic vascular resistance falls resulting in a drop in blood pressure. A reflex tachycardia is rare and propofol is usually associated with a bradycardia especially if administered with fentanyl or alfentanil. Sympathetic activity and myocardial contractility are also reduced.

• Respiratoryrespiratory depression leading to apnoea is common. It is rare to observe cough or laryngospasm following its use and so it is often used in anaesthesia for ease of placement of a laryngeal mask.

• Central nervous systemexcitatory effects have been associated with propofol in up to 10% of patients. They probably do not represent true cortical seizure activity; rather they are the manifestation of subcortical excitatoryinhibitory centre imbalance. The movements observed are dystonic with choreiform elements and opisthotonos. Propofol has been used to control status epilepticus.

• Gutit may possess anti-emetic properties when used to maintain anaesthesia for minor surgery where opioids are avoided.

• Paininjection into small veins is painful but may be reduced if lignocaine is mixed with propofol or if a larger vein is used.

• Metabolica fat overload syndrome, with hyperlipidaemia, and fatty infiltration of heart, liver, kidneys and lungs can follow prolonged infusion.

• Miscellaneousit may turn urine green.

Kinetics

Propofol is 98% protein-bound to albumin and has the largest volume of distribution of all the induction agents at 4l.kg1. Following bolus administration, its duration of action is short due to the rapid decrease in plasma levels as it is distributed to well-perfused tissues.

Metabolism is largely hepatic; about 40% undergoing conjugation to a glucuronide and 60% metabolized to a quinol, which is excreted as a glucuronide and sulphate, all of which are inactive and excreted in the urine. Its clearance exceeds hepatic blood flow suggesting some extra-hepatic metabolism. Owing to this high clearance, plasma levels fall more rapidly than those of thiopentone following the initial distribution phase. Its terminal elimination half-life is 512 hours although it has been suggested that when sampling is performed for longer than 24 hours the figure approaches 60 hours and may reflect the slow release of propofol from fat. During prolonged infusion its context-sensitive half-time increases, although where the infusion has been titrated carefully, waking may still be relatively rapid.

Toxicity

Propofol has been associated with the unexpected deaths of a small number of children being ventilated for respiratory tract infection in intensive care. Progressive metabolic acidosis and unresponsive bradycardia lead to death. The serum was noted to be lipaemic. Further small studies have not demonstrated significant differences over other sedation protocols. However, it is not licensed for sedation in children or as maintenance of general anaesthesia in children under 3 years of age.

It does not appear to cause any adverse effects when given intra-arterially, although onset of anaesthesia is delayed.

Ketamine

Ketamine is a phencyclidine derivative.

Presentation and Uses

Ketamine is presented as a racemic mixture of two enantiomers: S(+) and R(), the former being about 3.5 times more potent than the latter. It is soluble in water forming an acidic solution (pH 3.55.5). Three concentrations are available: 10, 50 and 100 mg.ml1, and it may be given intravenously (12 mg.kg1) or intramuscularly (510 mg.kg1) for induction of anaesthesia. Intravenous doses of 0.20.5 mg.kg1 are used to provide analgesia during vaginal delivery and to facilitate the

positioning of patients with fractures before regional anaesthetic techniques are performed. It has been used via the oral and rectal route for sedation and also by intrathecal and epidural routes for analgesia. However, its use has been limited by unpleasant side-effects.

Mechanism of Action

Ketamine antagonizes the excitatory neurotransmitter glutamate at *N*-methyl-D-aspartate (NMDA) receptors within the central nervous system. It interacts with opioid receptors in a complex fashion, antagonizing μ receptors, while showing agonist actions at k and d receptors. In contrast with the other anaesthetic agents, it does not interact with GABA receptors.

Effects

• Cardiovascularketamine is unlike other induction agents in that it produces sympathetic nervous system stimulation, increasing circulating levels of noradrenaline and adrenaline. Consequently heart rate, cardiac output, blood pressure and myocardial oxygen requirements are all increased. However, it does not appear to precipitate arrhythmias. This indirect stimulation masks the mild direct myocardial depressant effects that ketamine would otherwise exert on the heart.

• Respiratorythe respiratory rate may be increased and laryngeal reflexes relatively preserved. A patent airway is often, but not always, maintained and increased muscle tone associated with the jaw may precipitate airway obstruction. It causes bronchodilation and may be useful for patients with asthma.

• Central nervous systemit produces a state of dissociative anaesthesia that is characterized by EEG evidence of dissociation between the thalamocortical and limbic systems. In addition, intense analgesia and amnesia are produced. The a rhythm is replaced by q and d wave activity. Ketamine is different from other intravenous anaesthetics because it does not induce anaesthesia in one armbrain circulation timecentral effects becoming evident 90 seconds after an intravenous dose. Vivid and unpleasant dreams, hallucinations and delirium may follow its use. These emergence phenomena may be reduced by the concurrent use of benzodiazepines or opioids. They are less common in the young and elderly and also in those left to recover undisturbed. Cerebral blood flow, oxygen consumption and intracranial pressure are all increased. Muscle tone is increased and there may be jerking movements of the limbs.

• Gutnausea and vomiting occur more frequently than after propofol or thiopentone. Salivation is increased requiring anticholinergic premedication.

Kinetics

Following an intravenous dose the plasma concentration falls in a bi-exponential fashion. The initial fall is due to distribution across lipid membranes while the slower phase is due to hepatic metabolism. Ketamine is the least well protein-bound (about 25%) of the intravenous anaesthetics and is demethylated to the active metabolite norketamine by hepatic P450 enzymes. Norketamine (which is 30% as potent as ketamine) is further metabolized to inactive glucuronide metabolites. The conjugated metabolites are excreted in the urine.

Etomidate

Etomidate is an imidazole derivative and an ester.

Presentation

Etomidate is prepared as a 0.2% solution at pH of 4.1 and contains 35% v/v propylene glycol to improve stability and reduce its irritant properties on injection.

Uses

Etomidate is used for the induction of general anaesthesia at a dose of 0.3 mg.kg1.

Effects

At first glance etomidate would appear to have some desirable properties, but due to its side-effects its place in anaesthesia has remained limited.

Table 7.3: Pharmacological properties of some intravenous anaesthetics.

	Thiopentone	Methohexitone	Propofol	Ketamine	Etomidate
BP	–	–	– –		®
CO	–	–	– –		®
HR			– ®		®
SVR	–	–	– –	®	®
RR	–	–	–		–
ICP	–	–	–		®
IOP	–	–	–		®
Pain on injection	no	yes	yes	no	yes
Nausea and vomiting	no	no	? reduced	yes	yes

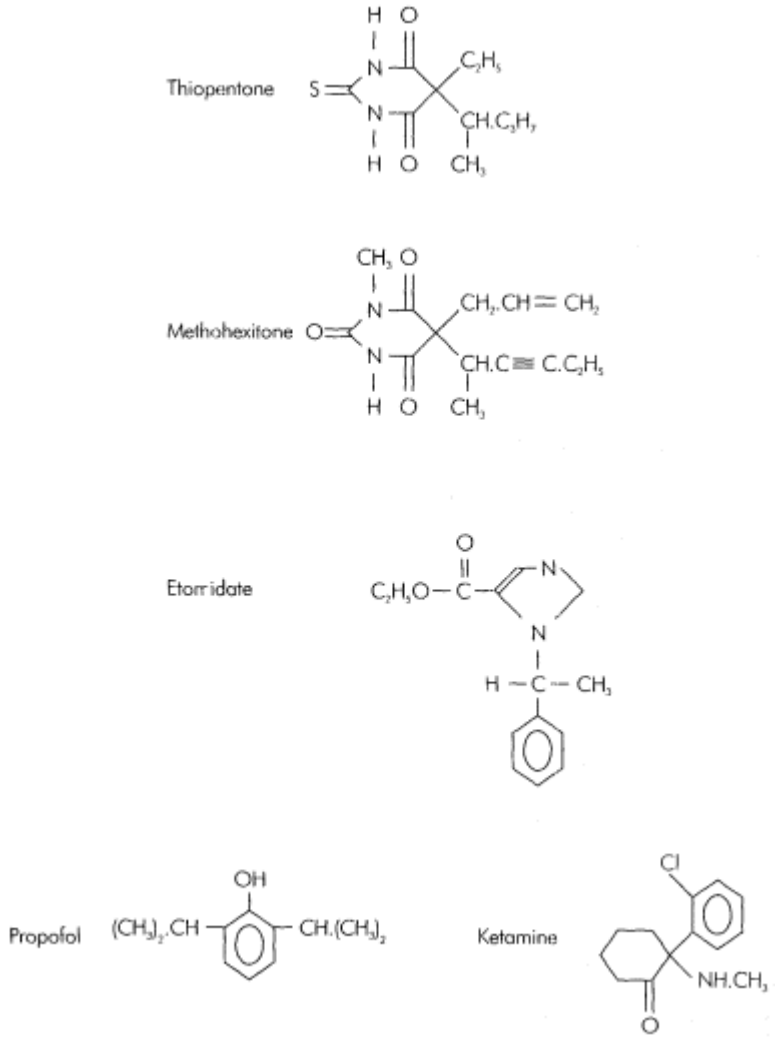


Figure 7.4:
Chemical structure of some intravenous anaesthetics.

• Cardiovascularof the commonly used intravenous anaesthetics it produces the least cardiovascular disturbance. The peripheral vascular resistance may fall slightly (but less so than with other induction agents), while myocardial oxygen supply, contractility and blood pressure remain largely unchanged. Hypersensitivity reactions are less common following etomidate and histamine release is rare.

• Metabolicit suppresses adrenocortical function by inhibition of the enzymes 11b-hydroxylase and 17a-hydroxylase, resulting in inhibition

of cortisol and aldosterone synthesis. It was associated with an increase in mortality when used as an infusion to sedate septic patients in intensive care. Single doses can influence adrenocortical function but are probably of little clinical significance in otherwise fit patients.

• Miscellaneousunpleasant side-effects relate to pain on injection in up to 25% of patients, excitatory movements and nausea and vomiting. It may also precipitate a porphyric crisis.

Kinetics

Etomidate is 75% bound to albumin. Its actions are terminated by rapid distribution into tissues, while its elimination from the body depends on hepatic metabolism and renal excretion. Non-specific hepatic esterases and possibly plasma cholinesterase, hydrolyse etomidate to ethyl alcohol and its carboxylic acid metabolite. It may also inhibit plasma cholinesterase.

Adverse Reactions to Anaesthetic Agents

An adverse reaction to a drug is one that is of no benefit to the patient. It may be considered as either:

• Dose-related, i.e. an extension of the known actions of the drug (e.g. too much propofol will cause hypotension).

• Non-dose-related, where even very small amounts may precipitate the reaction, which bears no relation to the normal actions of the drug. These reactions are generally the most serious.

• Related to a genetic idiosyncrasy (e.g. suxamethonium apnoea).

Anaphylactic and anaphylactoid reactions are not dose-related and are clinically indistinguishable. The offending drug is often hidden in a cocktail of other anaesthetic agents. Neuromuscular blocking agents cause the most anaphylactic reactions and are mainly due to suxamethonium. Methohexitone causes more reactions than thiopentone but these are often less severe. Most of the reactions due to thiopentone and morphine are anaphylactoid in nature. Antibiotics, latex, colloids and benzodiazepines produce severe reactions less frequently.

• An anaphylactic reaction is an exaggerated response to a foreign substance to which the patient has become previously sensitized. Subsequent exposure results in binding to specific IgE and subsequent release of histamine and other vasoactive amines.

• An anaphylactoid reaction is clinically indistinguishable from an anaphylactic reaction but is triggered by direct stimulation of histamine release or alternative complement activation. It does not involve IgE and no prior exposure is necessary.

Tryptase, which is found almost exclusively in mast cells, is released during these reactions and reaches a peak at about 1 hour. When raised it confirms the clinical picture as anaphylactic or anaphylactoid.

The incidence of anaphylactic and anaphylactoid reactions is hard to estimate and depends on reporting. Women are three to four times more frequently affected and the incidence in the UK lies somewhere between 1:600020 000. Latex is increasingly being recognized as a serious cause of anaphylaxis.

Treatment of an Anaphylactic Reaction

Treatment of an anaphylactic reaction involves:

• Initial therapystop giving the suspected drug, call for help, maintain a patent airway and administer 100% O2 The patient should be laid flat with their legs elevated. Adrenaline and intravenous fluids should be given until a response has been obtained.

• Secondary therapyantihistamines, steroids, catecholamine infusions, bicarbonate following estimation of arterial pH) and bronchodilators.

Blood (10 ml) should be taken 1 hour after the onset and stored at 20°C for serum tryptase levels. The anaesthetist is responsible for organizing the further investigation of the patient, including skin prick testing.

8
Inhaled Anaesthetics

Agents in current use include the gas nitrous oxide (N2O) and the volatile liquids isoflurane, halothane, enflurane, desflurane and sevoflurane. Ether and cyclopropane are now not used in the UK. Xenon has useful properties but is expensive to extract from the atmosphere, which currently limits its clinical use. Their mechanism of action is not clear.

The MeyerOverton hypothesis (proposed nearly a century ago) demonstrated a link between lipid solubility (oil:gas solubility coefficient) and potency (MAC) (Figure 8.1), and suggested that when a sufficient amount of drug dissolved into a neuronal lipid membrane anaesthesia occurred. This may be due to ion channel distortion preventing synaptic transmission. However, more recent research has

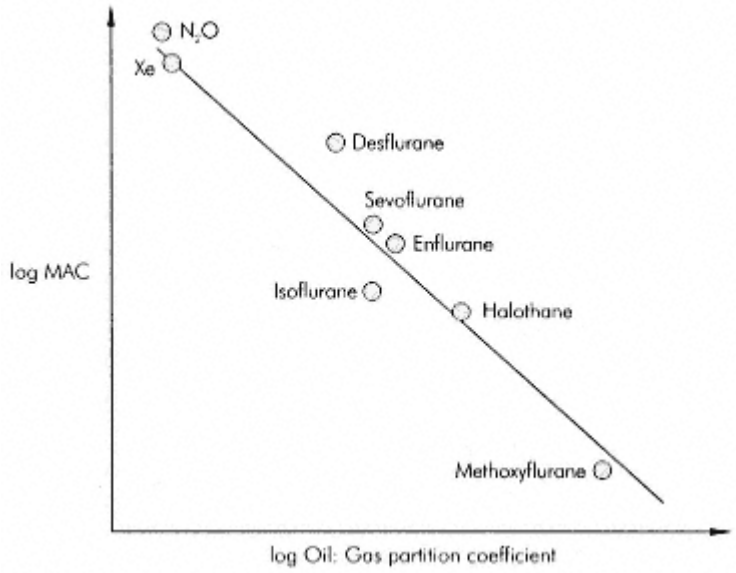


Figure 8.1:
Straight line relationship between MAC and an index of lipid solubility (note: logarithmic scales).

suggested that volatile agents may interact with specific membrane proteins to alter ion channels or receptors. For example, the different enantiomers of isoflurane appear to have some stereoselectivity with regard to g-aminobutyric acid type A (GABAA) receptor binding, while having identical physiochemical properties.

Minimum Alveolar Concentration (MAC)

MAC is a measure of potency and is defined as the minimum alveolar concentration at steady-state that prevents reaction to a standard surgical stimulus (skin incision) in 50% of subjects at sea level (i.e. 1 atmosphere). When MAC is plotted against a measure of lipid solubility (oil:gas partition coefficient) using logarithmic scales the relationship obtained is linear. MAC is altered by many physiological and pharmacological factors (Table 8.1), and is additive when agents are administered simultaneously.

Table 8.1: Factors altering MAC.

Factors increasing MAC	Factors decreasing MAC
Infancy	During the neonatal period
	Increasing age
	Pregnancy
	Hypotension
Hyperthermia	Hypothermia
Hyperthyroidism	Hypothyroidism
Catecholamines and sympathomimetics	a2 agonists
	Sedatives
Chronic opioid use	Acute opioid use
Chronic alcohol intake	Acute alcohol intake
Acute amphetamine intake	Chronic amphetamine intake
Hypernatraemia	Lithium

The Ideal Volatile Anaesthetic Agent

While the agents in use today demonstrate many favourable characteristics, no single agent has all the desirable properties listed below. 'Negative' characteristics (e.g. not epileptogenic) are simply a reflection of a currently used agent's side-effect.

Physical

- stable to light and heat
- inert when in contact with metal, rubber and soda lime
- preservative free

- not flammable or explosive
- pleasant odour
- atmospherically friendly
- cheap

Biochemical

- high oil:gas partition coefficient; low MAC
- low blood:gas partition coefficient
- not metabolized
- non-toxic
- only affects the CNS
- not epileptogenic
- some analgesic properties

Kinetics of Inhaled Anaesthetics

At steady-state, the partial pressure of inhaled anaesthetic within the alveoli (PA) is in equilibrium with that in the arterial blood (Pa) and subsequently the brain (PB). Therefore, PA gives an indirect measure of PB. However, for most inhaled anaesthetics steady-state is rarely achieved in the clinical setting as the process may take many hours (Figure 8.2).

Physiological and agent-specific factors influence the speed at which inhaled anaesthetics approach equilibrium.

- Alveolar ventilation

Increased alveolar ventilation results in a faster rise in PA. Consequently PB increases more rapidly and so the onset of anaesthesia is faster. A large functional residual capacity (FRC) will effectively dilute the inspired concentration and so the onset of anaesthesia will be slow. Conversely, those patients with a small FRC have only a small volume with which to dilute the inspired gas and so PA rises rapidly resulting in a fast onset of anaesthesia.

- Inspired concentration

A high inspired concentration leads to a rapid rise in PA and so onset of anaesthesia is also rapid.

- Cardiac output

A high cardiac output will tend to maintain a concentration gradient between the alveolus and the pulmonary blood so that PA rises slowly. Conversely, a low cardiac

output favours a more rapid equilibration and so onset of anaesthesia will also be more rapid.

- Blood:gas partition coefficient

The blood:gas partition coefficient is defined as the ratio of the amount of anaesthetic in blood and gas when the two phases are of equal volume and pressure and in equilibrium at 37°C.

While it might be expected that agents with a high blood:gas partition coefficient (i.e. high solubility) would have a rapid onset, this is not the case because these agents only exert a low partial pressure in blood, even when present in large amounts. It is the partial pressure of the agent in the blood and subsequently the brain that gives rise to anaesthesia and not the total amount present. Agents with a low blood:gas partition coefficient exert a high partial pressure and will, therefore, produce a more rapid onset and offset of action. While a low blood:gas partition coefficient is important, MAC and respiratory irritability can also alter the speed of induction.

- Concentration and second gas effect

These are described under nitrous oxide (p86).

Metabolism

Hepatic cytochrome P450 metabolizes the C-(halogen) bond to release halogen ions (F, C1 Br), which may cause hepatic or renal damage. The C-F bond is a stable one and is only minimally metabolized unlike C-Cl, C-Br and C-I which become progressively easy to metabolize (Table 8.2).

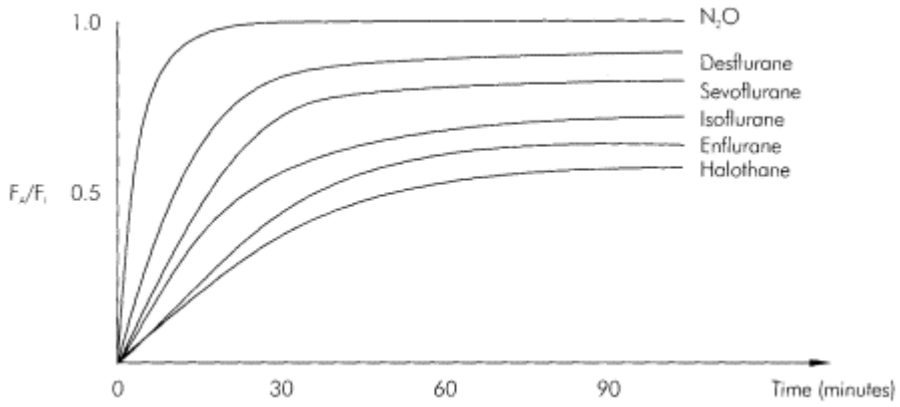


Figure 8.2:
Different agents approach a FA/FI, ratio of 1 at different rates. Agents with a low blood:gas partition coefficient reach equilibrium more rapidly.
(FA/FI, represents the ratio of alveolar concentration to inspired concentration).

Table 8.2: Metabolism of inhaled anaesthetic agents.

Agent	Percentage metabolized	Metabolites
N2O	< 0.01	(N2)
Halothane	20	Trifluoroacetic acid, Cl, Br
Sevoflurane	3.5	Inorganic and organic fluorides Compound A in the presence of soda lime and heat (Compound B, C, D and E)
Enflurane	2	Inorganic and organic fluorides
Isoflurane	0.2	Trifluroacetic acid and F
Desflurane	0.02	Trifluroacetic acid

Inhaled Anaesthetics

Nitrous Oxide (N2O)

N2O is used widely alongside the volatile agents and in combination with oxygen (O2) as entonox. Apart from a high MAC it has favourable physical properties. However, during even relatively short exposure it interferes with DNA synthesis and increasing concern over this and other aspects of N2O may limit its future use.

Manufacture

N2O is manufactured by heating ammonium nitrate to 250°C.

$$NH_4NO_3 \rightarrow N_2O + 2H_2O.$$

Unless the temperature is carefully controlled N2O may contain the following contaminants: NH3, N2, NO, NO2, and HNO3. These impurities are actively removed by passage through scrubbers, water and caustic soda.

Storage

It is stored as a liquid in French blue cylinders (C = 450 litres up to G = 9000 litres) with a gauge pressure of 51 bar at 20°C, which, therefore, bears no correlation to cylinder content until all remaining N2O is in the gaseous phase. The filling ratio (mass of N2O in cylinder/mass of water that the cylinder could hold) is 0.75 in temperate regions, but it needs to be reduced to 0.67 in tropical regions to avoid cylinder explosions. Its critical temperature is 36.5°C; its critical pressure is 72 bar.

Effects

- Respiratoryit causes a small fall in tidal volume that is offset by an increased respiratory rate so that minute volume and PaCO2 remain unchanged.

• Cardiovascularwhile N2O has mild direct myocardial depressant effects it also increases sympathetic activity by its central effects. Therefore, in health the circulatory system is changed very little. However, for patients with cardiac failure who are unable to increase their sympathetic drive the direct myocardial depressant effects may significantly reduce cardiac output. It does not sensitize the heart to catecholamines.

• Central nervous systemN2O increases cerebral blood flow and is sometimes avoided in patients with a raised intracranial pressure. Despite a MAC = 105%, its potential to cause anaesthesia in certain patients should not be ignored.

Concentration Effect, Second Gas Effect and Diffusion Hypoxia

Owing to its low blood:gas partition coefficient its onset and offset of action are very rapid. However, it is about 20 times more soluble than O2 and N2 and consequently during induction with high concentrations of N2O, the volume of N2O entering the pulmonary capillaries will be greater than the volume of N2 entering the alveolus. The volume of the alveolus decreases, thereby increasing the fractional concentrations of the remaining gases.

The concentration effect refers to the disproportionate increase in alveolar partial pressure and its rate of approximation to the inhaled concentration. It only applies to N2O as it is the only agent given in sufficient concentration. It is a result of two processes. First, the concentrating effect of the rapid N2O uptake and, second, augmented ventilation as bronchial and tracheal gas is drawn into the alveolus to make good the diminished alveolar volume.

The second gas effect is a result of the concentration effect. Volatile agents used alongside high concentrations of N2O will be concentrated by both elements of the concentration effect, resulting in a higher alveolar partial pressure and a reduced induction time.

At the end of anaesthesia when N2O/O2 is replaced by N2/O2 the reverse effect is seen. The volume of N2O entering the alveolus will be greater than the volume of N2 entering the pulmonary capillaries resulting in a dilution of all alveolar gases. If supplemental O2 were not routinely administered at this stage diffusion hypoxia would result.

In addition to the effects seen across the alveolar membrane, N2O will cause a rapid expansion of any air filled space (pneumothorax, vascular air embolus and intestinal lumen).

Toxicity

The cobalt ion present in vitamin B12 is oxidized by N2O so that it is no longer able to act as the cofactor for methionine synthase (Figure 8.3). The result is reduced

synthesis of methionine, thymidine, tetrahydrofolate and DNA. Methionine synthetase also appears to be directly inhibited by N2O. Exposure lasting only a few hours may result in megaloblastic changes in the bone marrow but more prolonged exposure (i.e. days) may result in agranulocytosis. Recovery is governed by synthesis (taking a few days) of new methionine synthase, but may be helped by the administration of folinic acid, which provides a different source of tetrahydrofolate.

In a properly scavenged environment where N2O concentrations are less than 50 ppm there is no effect on DNA synthesis. However, in unscavenged dental surgeries where large amounts are used, chronic exposure may result in neurological syndromes that resemble subacute combined degeneration of the cord, as a result of chronic vitamin B12 inactivation.

In experimental conditions N2O has been shown to be teratogenic to rats but this effect is prevented by folinic acid. While this has never been unequivocally demonstrated in humans, N2O is often not used in the first trimester when anaesthesia is required.

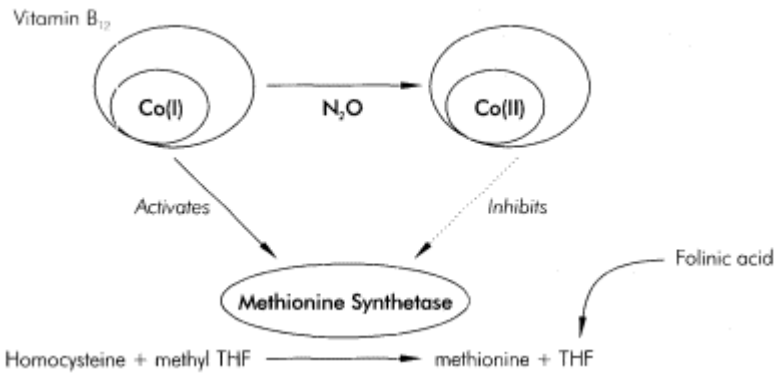


Figure 8.3:
N2O inhibits methionine synthetase by
oxidizing cobalt (Co(I)). THF, tetrahydrofolate.

Entonox

This is a 50:50 mixture of N2O and O2. The two gases effectively dissolve into each other and do not behave in a way that would be predicted from their individual properties. This phenomenon is called the Poynting effect.

Uses

Entonox is widely used for analgesia during labour and other painful procedures.

Storage

Entonox is stored as a gas in French blue cylinders (G = 3200 litres; J = 6400 litres) with white and blue checked shoulders at 137 bar. It separates into its constituent parts below its pseudo-critical temperature, which is about 7°C and is most likely to occur at 117 bar. Higher or lower pressures reduce the likelihood of separation. When delivered via pipeline at 4.1 bar the pseudo-critical temperature is less than 30°C. If a cylinder is used following separation, the inspired gas will initially produce little analgesia as it contains mainly O2, but as the cylinder empties the mixture will become progressively potent and hypoxic as it approaches 100% N2O.

Halothane

This halogenated hydrocarbon is unstable when exposed to light, and it corrodes certain metals. It is stored with thymol (0.01%) to prevent the liberation of free bromine. It dissolves into rubber and may leach out into breathing circuits after the vaporizer is turned off. Its physical properties are summarized in Table 8.3.

Effects

• Respiratorythe minute ventilation is depressed largely due to a decreased tidal volume. The normal responses to hypoxia and hypercarbia are also blunted and these effects are more pronounced above 1 MAC. Bronchiolar tone is reduced and it is useful in asthmatic patients. Owing to its sweet non-irritant odour it may be used to induce anaesthesia.

• Cardiovascularhalothane has significant effects on the heart. Bradycardia is produced by increased vagal tone, depressed sino-atrial

Table 8.3: Physiochemical properties of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane	N2O	Xenon
MW	197.0	184.5	184.5	168.0	200.1	44.0	131.0
BP (°C)	50.2	48.5	56.5	23.5	58.5	88.0	108
SVP at 20°C (kPa)	32.3	33.2	23.3	89.2	22.7	5200	
MAC (%)	0.75	1.17	1.68	6.60	1.80	105	71.0
Blood:gas partition coefficient	2.40	1.40	1.80	0.45	0.70	0.47	0.14
Oil:gas partition coefficient	224	98	98	29	80	1.4	
Odour	non-irritant, sweet	irritant	non-irritant	pungent	non-irritant	odourless	odourless

and atrio-ventricular activity. It has direct myocardial depressant properties that reduce cardiac output. It sensitizes the heart to catecholamines, which may lead to arrhythmias (especially ventricular and bradyarrhythmias) and are more common than with other agents. Where adrenaline is infiltrated to improve the surgical field less than 100 µg per 10 minutes should be given. Drugs that specifically reduce atrio-ventricular conductivity (e.g. verapamil) should be used with caution alongside halothane. The systemic vascular resistance is reduced resulting in increased cutaneous blood flow. However, due to a reduced cardiac output blood flow to the liver and kidneys is reduced.

• Central nervous systemcerebral blood flow is increased more than with any other volatile agent leading to significant increases in intracranial pressure above 0.6 MAC. Cerebral oxygen requirements are reduced.

Metabolism

Up to 25% of inhaled halothane undergoes oxidative metabolism by hepatic cytochrome P450 to produce trifluoroacetic acid, Br and Cl. However, reductive metabolism producing F and other reduced metabolites predominate when the liver becomes hypoxic. While these reduced metabolites are toxic it is thought that they are not involved in halothane hepatitis.

Toxicity

Hepatic damage may take one of two forms:

• A reversible form that is often subclinical and associated with a rise in hepatic transaminases. This is probably due to hepatic hypoxia.

• Fulminant hepatic necrosis (halothane hepatitis). Trifluoroacetyl chloride (an oxidative metabolite of halothane) may behave as a hapten, binding covalently with hepatic proteins, inducing antibody formation. The diagnosis of halothane hepatitis is based on the exclusion of all other forms of liver damage. The incidence in children is between 1 in 80 000200 000 while in the adult it is 1 in 250035 000. The following are risk factors: multiple exposures, obesity, middle age and female sex. The mortality rate is 5075%.

Halothane should be avoided if administered within the previous 3 months, there is a history of a previous adverse reaction to halothane or pre-existing liver disease.

Enflurane has also been reported to cause hepatic necrosis. Its incidence is much lower due to its lower rate of metabolism. In theory the other volatile agents may cause a similar reaction but due to their even lower rates of metabolism this becomes increasingly unlikely.

Isoflurane

This halogenated ethyl methyl ether is a structural isomer of enflurane. It is widely used to maintain anaesthesia. Its physical properties are summarized in Table 8.3.

Effects

• Respiratoryisoflurane depresses ventilation more than halothane but less than enflurane. Minute volume is decreased while respiratory rate and PaCO2 are increased. It is rarely used to induce anaesthesia due to its pungent smell, which may cause upper airway irritability, coughing and breath-holding. However, despite its pungent smell it causes some bronchodilation.

• Cardiovascularits main effect is to reduce systemic vascular resistance. The resulting reflex tachycardia suggests that the carotid sinus reflex is preserved. It causes only a small decrease in myocardial contractility and cardiac output. Isoflurane is a more potent coronary artery vasodilator than the other volatile agents and may cause coronary steal whereby normally responsive coronary arterioles are dilated and divert blood away from areas supplied by unresponsive diseased vessels, resulting in ischaemia.

• Central nervous systemof all the volatile agents isoflurane produces the best balance of reduced cerebral oxygen requirement and minimal increase in cerebral blood flow. At concentrations up to 1 MAC cerebral autoregulation is preserved.

Metabolism

Only 0.2% is metabolized and none of the products has been linked to toxicity.

Toxicity

Owing to the presence of a -CHF2 group in its structure it may react with dry soda lime (or baralyme) producing carbon monoxide. Reports of this relate to circle systems that have been left with dry gas circulating over a weekend so that subsequent use of isoflurane causes release of carbon monoxide. Enflurane and desflurane also possess -CHF2 groups and may react in a similar manner.

Enflurane

This halogenated ethyl methyl ether is a structural isomer of isoflurane. Its use is decreasing due to newer agents with more favourable profiles.

Effects

• Respiratoryenflurane causes more depression of ventilation than the other agents. The minute volume decreases and the PaCO2 will rise. The ventilatory response to hypoxia and hypercarbia are also blunted.

• Cardiovascularwhile the heart rate increases, the cardiac contractility, output and blood pressure fall along with a small fall in systemic vascular resistance. The heart is not sensitized to catecholamines, and arrhythmias are relatively uncommon.

• Central nervous systemhigh concentrations of enflurane in the presence of hypocarbia produce a 3 Hz spike and wave pattern consistent with grand mal activity. While there is no evidence that these changes are seen more frequently in epileptics, enflurane is usually avoided in this group of patients. The increase in cerebral blood flow and accompanying increase in intracranial pressure lie between those observed with halothane and isoflurane.

Metabolism

Only 2% is metabolized by hepatic cytochrome P450. F ions are produced but rarely reach the levels (> 40 µmol.11) known to produce reversible nephropathy. It is usually avoided in patients with renal impairment.

Toxicity

Hepatic damage may occur (cf. halothane metabolism).

Desflurane

Desflurane (a fluorinated methyl ethyl ether) was slow to be introduced into anaesthetic practice due to difficulties in preparation and administration. It has a boiling point of 23.5°C, which renders it extremely volatile and, therefore, dangerous to administer via a conventional vaporizer. It is, therefore, administered via the electronic Tec 6 vaporizer that heats desflurane to 39°C at 2 atmospheres. Its low blood:gas partition coefficient (0.47) ensures a rapid onset and offset, but high concentrations are required due to its MAC of 6.6%.

Effects

• Respiratorydesflurane shows similar respiratory effects to the other agents, being more potent than halothane but less potent than isoflurane and enflurane. PaCO2 rises and minute ventilation falls with increasing concentrations. Desflurane has a pungent odour that causes coughing and breath holding. It is not suitable for induction of anaesthesia.

• Cardiovasculartheese may be thought of as similar to isoflurane. However, in patients with ischaemic heart disease particular care is required as concentrations above 1 MAC may produce cardiovascular stimulation (tachycardia and hypertension). It does not sensitize the

heart to catecholamines. Vascular resistance to both cerebral and coronary circulations is decreased.

Metabolism

Only 0.02% is metabolized and so its potential to produce toxic effects is minimal.

Sevoflurane

This polyfluorinated isopropyl methyl ether has the favourable combination of a relatively low blood:gas partition coefficient (0.65), pleasant odour and relatively low MAC (1.8). However, concerns over its metabolism have delayed widespread introduction into general anaesthetic practice. Unlike the other volatile agents sevoflurane is achiral.

Effects

• Respiratorysevoflurane is a useful agent for induction of anaesthesia due to its pleasant odour and favourable physical properties. It does, however, depress ventilation in a predictable fashion with a reduction in minute volume and a rise in PaCO2.

• Cardiovascularthe systemic vascular resistance falls and, due to an unchanged heart rate, the blood pressure falls. Cardiac contractility is unaffected and the heart is not sensitized to catecholamines. Vascular resistance to both cerebral and coronary circulations is decreased.

Metabolism

Sevoflurane undergoes hepatic metabolism by cytochrome P450 (isoform 2E1) to a greater extent than all the other commonly used volatile agents expect halothane. Hexafluoroisopropanol and inorganic F (known to cause renal toxicity) are produced. The now obsolete volatile anaesthetic methoxyflurane was also metabolized by hepatic P450 releasing F, and when plasma levels rose above 50 µmol.l1 renal toxicity was observed. However, renal toxicity is not observed following sevoflurane administration even when plasma levels reach 50 µmol.l1. A possible explanation lies in the additional metabolism of methoxyflurane by renal P450 to F, which generates a high local concentration while sevoflurane undergoes little or no renal metabolism.

Toxicity

When sevoflurane is administered in a circle system using soda lime or baralyme a number of compounds are produced. Compounds A, B, C, D and E have all been identified although only compounds A and B (which is less toxic) are present in sufficient quantities to make analysis feasible. The lethal concentration in 50% of rats is 300400 ppm after 3 hours exposure. Extrapolation of these and other animal studies suggest a human nephrotoxic threshold of 150200 ppm. Recent work

suggests that even with flow rates of 0.25 l.min1 for 5 hours the level of compound A peaks at less than 20 ppm and is not associated with abnormal tests of renal function.

Concentrations of compound A may increase with increased levels of sevoflurane and increased temperature of CO2 absorbent, especially when baralyme is used in place of soda lime.

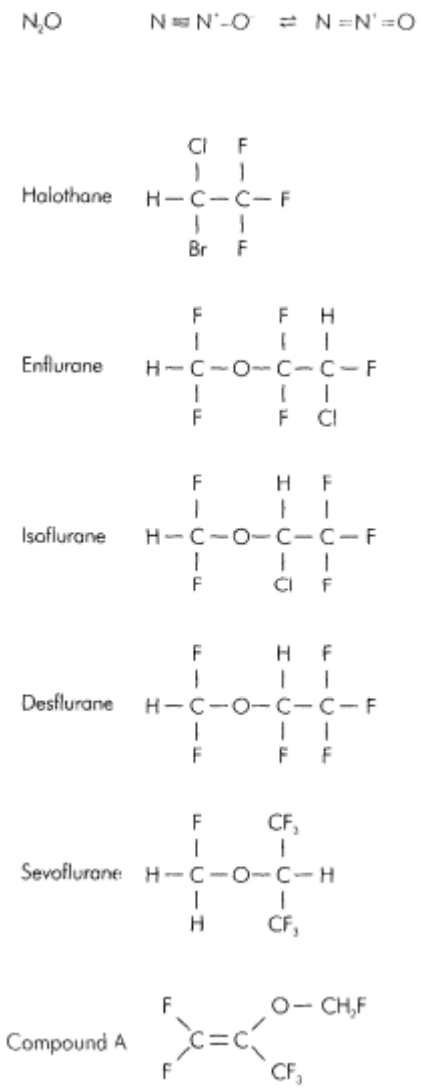


Figure 8.4:
Structure of some inhaled anaesthetics and Compound A.

Xenon (Xe)

Xenon is an inert, odourless gas with no occupational or environmental hazards and makes up 0.0000087% of the atmosphere. It has a MAC = 71% and a very low blood:gas partition coefficient (0.14). Consequently, its onset and offset of action are faster than both desflurane and N2O.

Manufacture

Xe is produced by the fractional distillation of air, at about 2000 times the cost of producing N2O.

Effects

- Respiratoryin contrast to the other inhaled anaesthetic agents the respiratory rate is slowed, while the tidal volume is increased so that the minute volume remains constant. Compared with N2O, Xe has a higher density (×3) and viscosity (×1.5) which might be expected to increase airway resistance when used in high concentrations. However, its clinical significance is probably minimal. Despite its use at high concentrations it does not appear to result in diffusion hypoxia in a manner similar to that seen with N2O.

- CardiovascularXe does not alter myocardial contractility but may result in a small decrease in heart rate.

- Central nervous systemXe may be used to enhance CT images of the brain while 133Xe may be used to measure cerebral blood flow. However, in humans it appears to increase the cerebral blood flow in a variable manner, and its use in anaesthesia for neurosurgery is not recommended.

- Analgesiait has significant analgesic properties.

Table 8.4: Cardiovascular effects of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Contractility	↓	↓	↓	minimal ↓	↓
Heart rate	↓	↑	↑	↑ (> MAC)	nil
Systemic vascular resistance	↓	↓	↓	↓	↓
Blood pressure	↓	↓	↓	↓	↓
Coronary steal syndrome	no	possibly	no	no	no
Splanchnic blood flow	↓	unchanged	↓	unchanged	unchanged
Sensitization to catecholamines	↑↑	nil	↑	nil	nil

Table 8.5: Respiratory effects of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Respiratory Rate	_	—	——	—	_
Tidal volume					
PaCO2	unchanged				

Table 8.6: Other effects of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Cerebral blood flow	_	(nil if < 1 MAC) _	_	_	_
Cerebral O2 requirement					
EEG	burst suppression	burst suppression	epileptiform activity (3 Hz spike and wave)	burst suppression	burst suppression
Effect on uterus	some relaxation	some relaxation	some relaxation	some relaxation	some relaxation
Potentiation of muscle relaxation	some	significant	significant	significant	significant
Analgesia	none	some	some	some	some

Elimination

Xe is not metabolized in the body, rather it is eliminated via the lungs.

Non-Anaesthetic Medical Gases

Oxygen (O2)

Manufacture and Storage

Oxygen is manufactured by the fractional distillation of air or by means of an oxygen concentrator in which a zeolite mesh adsorbs N2 so that the remaining gas is about 97% O2. It is stored as a gas in black cylinders with white shoulders at 137 bar and as a liquid in a vacuum insulated evaporator (VIE) at 10 bar and 180°C, which must be located outside. The VIE rests on three legs, two are hinged while the third serves as a weighing device, enabling its contents to be displayed on a dial.

Physiochemical Properties

- Boiling point 182°C
- Critical temperature 119°C
- Critical pressure 50 bar

Uses

It is used to prevent hypoxaemia.

Measurement

Depending on the sample type, various means are used to measure O2. In a mixture of gases a mass spectrometer, paramagnetic analyser or fuel cell may be used; when dissolved in blood a Clarke electrode, transcutaneous electrode or pulse oximetry may be used; in vitro blood samples may be analysed by bench or co-oximetry.

Effects

• Cardiovascularif O2 is being used to correct hypoxaemia then an improvement in all cardiovascular parameters will be seen. However, prolonged administration of 100% O2 will directly reduce cardiac output slightly and cause coronary artery vasoconstriction. It causes a fall in pulmonary vascular resistance and pulmonary artery pressure.

• Respiratoryin healthy subjects a high concentration causes mild respiratory depression. However, in those patients who are truly dependent on a hypoxic drive to maintain respiration, even a modest concentration of O2 may prove fatal.

Toxicity

O2 toxicity is caused by free radicals. They affect the nervous system resulting in anxiety, nausea and seizures when the partial pressure exceeds 200 kPa. The alveolar capillary membrane undergoes lipid peroxidation and regions of lung may collapse. Neonates are susceptible to retrolental fibroplasia, which may be due to vasoconstriction of developing retinal vessels during development.

Nitric Oxide (NO)

Nitric oxide is an endogenous molecule but it is potentially a contaminant in nitrous oxide cylinders. It was formerly known as endothelium-derived relaxing factor (EDRF).

Synthesis

NO is synthesized from one of the terminal guanidino nitrogen atoms of L-arginine in a process catalysed by nitric oxide synthase (NOS) (Figure 8.5). NOS is present in two forms:

• Constitutivewhich is normally present in endothelial, neuronal, skeletal muscle, cardiac tissue and platelets. Here NOS is Ca2+/calmodulin-dependent and is stimulated by cGMP.

Figure 8.5:
Synthesis of endogenous NO.

• Induciblewhich is seen only after exposure to endotoxin or certain cytokines in endothelium, vascular smooth muscle, myocytes, macrophages and neutrophils. Following induction large quantities of NO are produced which may be cytotoxic. In addition, it may form radicals leading to cellular damage and capillary leakage.

Effects

• Cardiovascularvasodilator tone in small arteries and arterioles is dependent on a continuous supply of locally synthesized NO. Shear stresses in these vessels increase NO production and may account for flow-dependent vasodilatation. NO derived from the endothelium inhibits platelet aggregation. In septic shock there is overproduction of NO resulting in hypotension and capillary leak.

• Respiratoryendogenous NO provides an important basal vasodilator tone in pulmonary and bronchial vessels, which may be reversed in hypoxia. When inhaled in concentrations of up to 40 ppm it may reduce V/Q mismatching in acute respiratory distress syndrome (ARDS) and reduce pulmonary hypertension in neonates. Inhaled NO has no effect on the systemic circulation due to its rapid inactivation within red blood cells. Its affinity for haemoglobin is 1500 times that of carbon monoxide. It has no bronchodilator properties.

• ImmuneNO synthesized in macrophages and neutrophils can be toxic to certain pathogens and may be an important host defence mechanism.

• HaematologicalNO inhibits platelet aggregation.

• Neuronalnerves containing NO are widely distributed throughout the central nervous system. Proposed roles include modulation of the state of arousal, pain perception, programmed cell death and long-term neuronal depression and excitation whereby neurones may 'remember' previous signals. Peripheral neurones containing NO control regional blood flow in the corpus cavernosum.

N-monomethyl-L-arginine (L-NMMA) is a guanidino substituted analogue of L-arginine which inhibits NOS. While L-NMMA has been used to antagonize NOS,

resulting in an increased blood pressure in septic shock, it does not alter the course of the underlying pathology and has not been shown to alter survival.

Sodium nitroprusside and the organic nitrates (e.g. glyceryl trinitrate) exert their effect by the spontaneous release of nitric oxide or metabolism to nitric oxide in smooth muscle cells.

UK Guidelines for the Use of Inhaled NO in Adult Intensive Care Units

An expert group of physicians and representatives from the department of health and industry issued the following guidelines in 1997:

Indications

- severe ARDSoptimally ventilated, PaO2 < 12 kPa with FIO2 = 1
- right-sided cardiac failure

Dose

- maximum = 40 ppm, but use minimum effective dose

Equipment

- a synchronized inspiratory injection system is considered optimal. If a continuous delivery system is used it must be through a calibrated flowmeter
- stainless steel pressure regulators and connectors should be used

Monitoring

- chemiluminescence or electrochemical analysers should be used and are accurate to 1 ppm
- methaemoglobinaemia is only very rarely significant and is more likely in paediatric patients or those with methaemoglobin reductase deficiency but levels should be checked before and after starting NO2 and daily thereafter

Exposure

- environmental NO levels should not exceed 25 ppm for 8 hours (time-weighted average)
- scavenging is not required in a well ventilated unit

Contraindications

- methaemoglobinaemia (bleeding diathesis, intracranial haemorrhage, severe LVF)

Helium (He)

Helium is an inert gas presented as either Heliox (79% He, 21% O2) in brown cylinders with white shoulders or as 100% helium in brown cylinders at 137 bar. It does not support combustion.

Its key physical characteristic is its lower density (and hence specific gravity) than both air and oxygen.

	Helium	Heliox	Oxygen	Air
Specific gravity	0.178	0.337	1.091	1

Therefore, during turbulent flow the velocity will be higher when Heliox is used. This will reduce the work of breathing and improve oxygenation in patients with an upper airway obstruction such as a tumour. Helium/oxygen mixtures are also used for deep water diving to avoid nitrogen narcosis. The lower density of helium/oxygen mixtures produces higher frequency vocal sounds, giving the typical squeaky voice.

Carbon dioxide (CO2)

Carbon dioxide is a colourless gas with a pungent odour at high concentrations. It is stored as a liquid at 51 bar at 20°C in grey cylinders (C = 450 litres up to E = 1800 litres). Its critical temperature is 31°C; its critical pressure is 73.8 bar.

Uses

It is used as the insufflating gas during laparoscopic procedures and occasionally to stimulate respiration following general anaesthesia. It is also used in cryotherapy.

Effects

- Cardiovascularby sympathetic stimulation it increases heart rate, blood pressure, cardiac output and dilates the coronary arteries. Arrhythmias are more likely in the presence of a raised PaCO2.

- Respiratorythe respiratory centre and peripheral chemoreceptors respond to a raised PaCO2 resulting in an increased minute volume and bronchodilation. However, a PaCO2 above 10 kPa may result in respiratory depression.

- Central nervous systemas PaCO2 rises so does cerebral blood flow and intracranial pressure. Beyond 10 kPa narcosis may ensue.

9
Analgesics

Pain has been defined in many different ways. At its core it is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Its perception is subject to many psychosocial factors and, therefore, varies between individuals.

Pain may become chronicwhere it outlasts any potential for healing and becomes modified centrally.

Physiology

Nociceptive impulses are triggered by the stimulation of nociceptors that respond to chemical, mechanical or thermal damage. The chemical mediators that initiate (H+, K+, acetylcholine, histamine, serotonin (5-HT), bradykinin), and sensitize (prostaglandins, leukotrienes, substance P, neurokinin A, calcitonin gene-related peptide) the nociceptors are legion. Two types of primary afferent fibres exist:

- small myelinated Ad fibres (diameter 25 µm) that conduct sharp pain rapidly (40 m.s1)
- unmyelinated C fibres (diameter < 2 µm) that conduct dull pain slowly (2 m.s1)

These fibres enter the dorsal horn of the spinal cord and synapse at different sites (Ad at Rexed laminae II and V; C at Rexed laminae II). The substantia gelatinosa (lamina II) integrates these inputs, from where second-order neurones form the ascending spinothalamic and spinoreticular pathways on the contralateral side. Descending pathways and the larger Ab fibres conducting 'touch' stimulate inhibitory interneurones within the substantia gelatinosa and inhibit C fibre nociceptive inputs. This forms the basis of the 'gate theory' of pain (Figure 9.1).

Pain may be modified by altering the neural pathway from its origin at the nociceptor to its interpretation within the central nervous system. The commonly used agents are discussed below under the following headings:

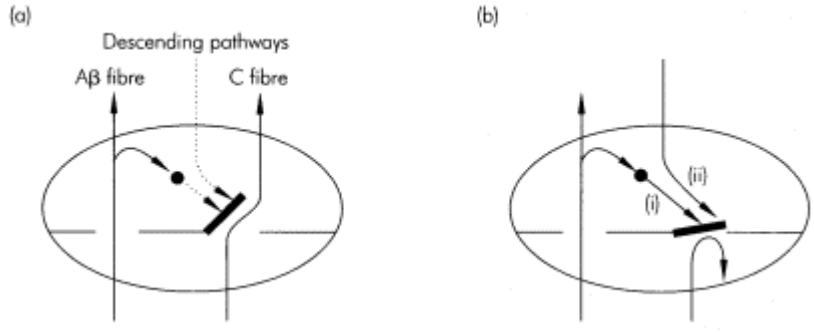


Figure 9.1:
Principle of the gate theory of pain within the dorsal horn of the spinal cord.
(a) Pain mediated via C fibres passes through the gate centrally;
(b) the gate is shut as Ab fibres stimulate inhibitory interneurones
(i) and by descending pathways, preventing the central passage of pain (ii).

- Opioids and related drugs
- Non-steroidal anti-inflammatory drugs (NSAID)

Other agents including local anaesthetics, antidepressants, anti-epileptics, guanethidine, ketamine and clonidine are discussed elsewhere.

Opioids and Related Drugs

The term 'opiate' refers to all naturally occurring substances with morphine like properties, while 'opioid' is a more general term that also includes synthetic substances that have an affinity for opioid receptors. Opioids are basic amines.

Receptor Classification

Opioid receptors have been divided into several subtypes (Table 9.1) and are distributed within the central nervous system, spinal cord and periphery. Their names follow the compound originally used to elicit certain syndromes in experiments on the dog. The classification originally included s receptors (prototype agonist N-allyl-normetazocine) that produced mydriasis, tachypnoea and delirium. They are no longer considered to be opioid receptors as they are not reversed by naloxone, exhibit high-affinity binding for ketamine and phencyclidine and are stereoselective for dextro-rotatory isomers while the other opioid receptors are stereoselective for laevo-rotatory isomers.

Opioid receptors are essentially presynaptic and activate Gi proteins leading to inhibition by increased K+ conductance and hyperpolarization of the cell membrane. They may also inhibit adenylate cyclase and Ca2+ channels.

Table 9.1: Classification of opioid receptors. A number of different subtypes of each receptor exist (two μ, three k, two d).

Receptor	Prototype agonist	Effects
μ1	morphine	analgesia, meiosis, euphoria
μ2	morphine	respiratory depression, bradycardia, inhibition of gut motility
k	ketocyclazacine	analgesia, sedation, meiosis
d	D-Ala, D-Leu enkephalin (DADL)	analgesia, respiratory depression

Morphine

Morphine is a naturally occurring phenanthrene derivative. It has a complex structure and is the reference opioid with which all others are compared.

Presentation and Uses

Morphine is formulated as tablets, suspensions and suppositories, and as slowrelease capsules and granules in a wide range of strengths. The parenteral preparation contains 1030 mg.ml1 and may be given intravenously or intramuscularly. The intramuscular dose is 0.10.2 mg.kg1 4 hourly. Intravenous morphine should be titrated to effect, but the total dose is similar. The subcutaneous route is avoided due to its relatively low lipid solubility. This is also the reason for the delayed respiratory depression, which may follow intrathecal or epidural administration.

Effects

- Analgesiaparticularly effective for visceral pain while less effective for sharp or superficial pain. Tolerance develops after repeated doses resulting in dependence.

- Respiratory depressionthe sensitivity of the brain stem to carbon dioxide is reduced following morphine. Its response to hypoxia is less affected but if this stimulus is removed by supplementary oxygen then respiratory depression may be potentiated. The respiratory rate falls more than the tidal volume. Morphine is anti-tussive. It may precipitate histamine release and bronchospasm.

- Nausea and vomitingthe chemoreceptor trigger zone is stimulated via 5-HT3 and dopamine receptors. The cells within the vomiting centre are depressed by morphine and do not stimulate vomiting.

- Central nervous systemsedation, euphoria and dysphoria occur with increasing doses.

- Circulatorymorphine may induce a mild bradycardia and hypotension secondary to histamine release and a reduction in sympathetic tone. It has no direct myocardial depressant effects.

• Gutmorphine constricts the sphincters of the gut. Constipation results from a state of spastic immobility of the bowel. The sphincter of Oddi is contracted by morphine thereby raising the pressure within the biliary tree.

• Histamine releasereducing the rate of administration will help to limit histamine-induced bronchospasm and hypotension. Histamine release may result in a rash and pruritus but this is easily reversed by naloxone.

• Pruritusmost marked following intrathecal or epidural use. However, this does not appear to be due to histamine release and is generally not associated with a rash. Paradoxically, antihistamines may be effective treatment for pruritus, possibly as a result of their sedative effects.

• Muscle rigidityoccasionally, morphine (and other opioids) can precipitate chest wall rigidity, which is thought to be due to opioid receptor interaction with dopaminergic and g-aminobutyric acid (GABA) pathways in the substantia nigra and striatum.

• Meiosisdue to stimulation of the EdingerWestphal nucleus, which can be reversed by atropine.

• Endocrinemorphine inhibits the release of adrenocorticotrophic hormone (ACTH), prolactin and gonadotrophic hormones. Antidiuretic hormone (ADH) secretion is increased and may cause impaired water excretion and hyponatraemia.

• Urinarythe tone of the bladder detrusor and vesical sphincter is increased and may precipitate urinary retention. Ureteric tone is also increased.

Kinetics

When given orally morphine is ionized in the acidic gastric environment (because it is a weak base, pKa = 8.0) so that absorption is delayed until it reaches the relatively alkaline environment of the small bowel where it becomes unionized. It undergoes extensive first-pass metabolism and only 25% reaches the systemic circulation. Its peak effects following intravenous or intramuscular injection are reached after 5 and 30 minutes respectively and it has a duration of action of 34 hours. It has been given by the epidural (24 mg) and intrathecal (0.21.0 mg) routes but this has been associated with delayed respiratory depression.

Morphine concentration in the brain falls slowly due to its low lipid solubility, and consequently plasma concentrations do not correlate with its effects.

Morphine metabolism occurs mainly in the liver but also in the kidneys. Up to 70% is metabolized to morphine 3-glucuronide which appears to have effects on arousal and is possibly a μ antagonist. The other major metabolite is morphine 6-

glucuronide, which is 13 times more potent than morphine and has a similar duration of action. They are both excreted in urine and accumulate in renal failure. Morphine is also N-demethylated. Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity, and in the elderly peak plasma levels are higher due to a reduced volume of distribution.

Diamorphine

Diamorphine is a diacetylated morphine derivative with no affinity for opioid receptors. It is a prodrug whose active metabolites are responsible for its effects. It is 1.52.0 times as potent as morphine.

Presentation and Uses

Diamorphine is available as 10 mg tablets and as a white powder for injection containing 5, 10, 30, 100 or 500 mg diamorphine hydrochloride, which is readily dissolved, before administration. It is used parenterally for the relief of severe pain, and dyspnoea associated with pulmonary oedema at 2.510 mg. It is used intrathecally (0.10.4 mg) and via the epidural route (13 mg) for analgesia where, due to a higher lipid solubility, it is less likely to cause delayed respiratory depression when compared with morphine.

Kinetics

Owing to its high lipid solubility it is well absorbed from the gut but has a low bioavailability due to an extensive first-pass metabolism. Its high lipid solubility enables it to be administered effectively by the subcutaneous route. Once in the plasma it is 40% protein-bound. It has a pKa = 7.6 so that 37% is in the unionized form at pH 7.4. Metabolism occurs rapidly in the liver, plasma and central nervous system by ester hydrolysis to 6-monoacetylmorphine and morphine, which confer its analgesic and other effects. The plasma half-life of diamorphine itself is very short (about 5 minutes).

It produces the greatest degree of euphoria of the opioids and subsequently has become a drug of addiction.

Papaveretum

Papaveretum is a semi-synthetic mixture of the anhydrous hydrochlorides of the alkaloids of opium. It contains morphine, codeine and papaverine. Noscapine was removed from its formulation after it had been shown to be teratogenic in animal studies, resulting in a standard dose of 15.4 mg, which is approximately equivalent to 10 mg morphine. It is not given via the intrathecal or epidural route due to preservatives. Its effects are essentially the same as morphine and are antagonized by naloxone.

Methadone

The notable feature of methadone is its relatively low first-pass metabolism resulting in a relatively high oral bioavailability of 75%. This enables it to be used orally, and as such it is used to treat those addicted to intravenous opioids, i.e. diamorphine, by means of slow weaning programs. It is less sedative than morphine.

Kinetics

It is 90% plasma protein-bound and metabolism occurs in the liver to a number of inactive metabolites. Up to 40% is excreted as unchanged drug in the urine, which is enhanced in acidic conditions.

Codeine

Codeine is 3-methoxymorphine. It is less potent than morphine and not suitable for severe pain. The oral and intramuscular dose is 3060 mg.

Kinetics

The presence of a methyl group reduces hepatic conjugation and so its oral bioavailability is 50%. About 10% is metabolized to morphine, while the rest is metabolized to inactive conjugated compounds. The metabolic route to morphine is dependent on an isoform of cytochrome P450 that exhibits polymorphism so that poor metabolizers may experience less pain relief.

Pethidine

Pethidine is a synthetic phenylpiperidine derivative originally designed as an anticholinergic agent, but was subsequently shown to have analgesic properties.

Presentation

Pethidine is available as tablets and as a solution for injection containing 1050 mg.ml1. The intravenous and intramuscular dose is 0.51.0 mg.kg1 and may be repeated 23 hourly. In common with all opioids the dose should be titrated to effect.

Uses

Pethidine is often used during labour. Its high lipid solubility enables significant amounts to cross the placenta and reach the foetus. Following its metabolism, the less lipid-soluble norpethidine accumulates in the foetus, levels peaking about 4 hours after the initial maternal intramuscular dose. Owing to reduced foetal clearance, the half-lives of both pethidine and norpethidine are prolonged up to three times.

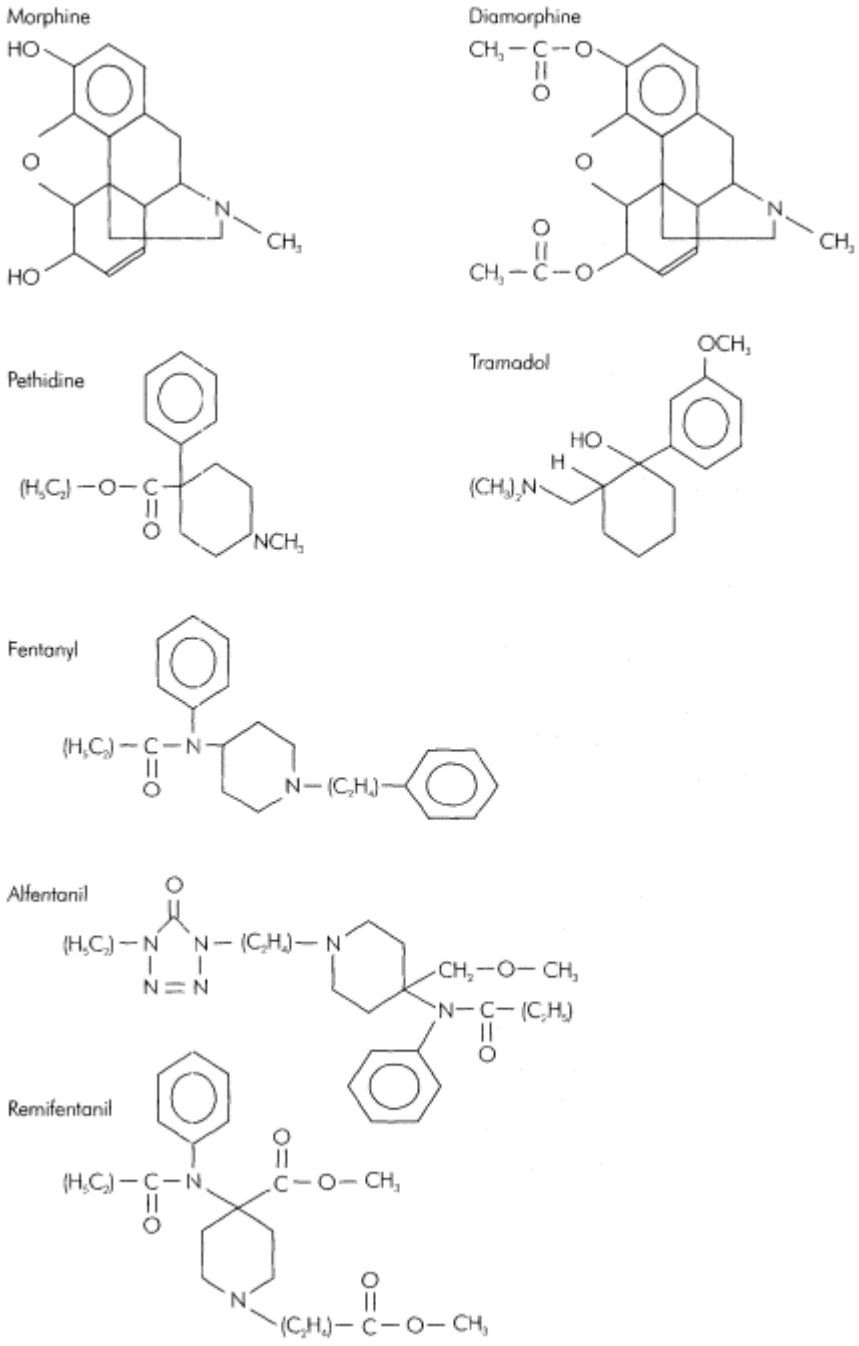


Figure 9.2:
Structure of some opioids.

Effects

Pethidine shares the common opioid effects with morphine. However, differences are seen:

• Anticholinergic effectsit produces less marked meiosis and possibly a degree of mydriasis, a dry mouth and sometimes tachycardia.

• Gutit is said to produce less biliary tract spasm than morphine.

• Interactionspethidine may produce a serious interaction if administered with monoamine oxidase inhibitors (MAOI). The mechanism of this interaction is not clear. Effects include coma, labile circulation, convulsions and hyperpyrexia. Other opioids are safe.

Kinetics

Pethidine is more lipid-soluble than morphine resulting in a faster onset of action. Oral administration has a bioavailability of 50%. It is metabolized in the liver by ester hydrolysis to the inactive pethidinic acid and by N-demethylation to norpethidine, which has half the analgesic activity of pethidine. Norpethidine has a longer elimination half-life (1421 hours) than pethidine and accumulates in renal failure. It has been associated with hallucinations and grand mal seizures following its accumulation. Its effects are not reversed by naloxone. Norpethidine and pethidinic acid are excreted in the urine along with small amounts of unchanged pethidine. The duration of action of pethidine is 120150 minutes.

Fentanyl

Fentanyl is a synthetic phenylpiperidine derivative with a rapid onset of action. It is a μ receptor agonist and as such shares morphine's effects. However, it is less likely to precipitate histamine release. High doses (50150 μg.kg1) significantly reduce or even eliminate the metabolic stress response to surgery, but are associated with bradycardia and chest wall rigidity.

Presentation

Fentanyl is prepared as a colourless solution for injection containing 50 μg.ml1 and as transdermal patches that release between 25 and 100 μg per hour for 72 hours.

Uses

Doses vary enormously depending on the duration of analgesia and sedation required. 12 μg.kg1 is used intravenously for pain associated with minor surgery and has a duration of about 30 minutes. Higher doses are generally required to obtund the stimulation of laryngoscopy. High doses (50100 μg.kg1) are used for an opioid-based anaesthetic, and here its duration of action is extended to about 6 hours. Its half-life is also significantly prolonged when given by continuous infusion.

Fentanyl has also been used to augment the effects of local anaesthetics in spinal and epidural anaesthesia at 1025 µg and 25100 µg respectively. Its high lipid solubility ensures that typical intrathecal doses do not cause delayed respiratory depression as it diffuses rapidly from cerebrospinal fluid (CSF) into the spinal cord. This contrasts with morphine, which enters the spinal cord slowly leaving some to be transported in the CSF by bulk flow up to the midbrain. However, respiratory depression is observed when epidural fentanyl is administered by continuous infusion or as repeated boluses.

Kinetics

Its onset of action is rapid following intravenous administration due to its high lipid solubility (nearly 600 times more lipid-soluble than morphine). However, following the application of a transdermal patch, plasma levels take 12 hours to reach equilibrium. At low doses (< 3 µg.kg1 intravenous) its short duration of action is due solely to distribution. However, following prolonged administration or with high doses, its duration of action is significantly prolonged as tissues become saturated. Its clearance is similar to that of morphine while its elimination half-life is longer reflecting its higher lipid solubility and volume of distribution. Fentanyl may become trapped in the acidic environment of the stomach where more than 99.9% is ionized. As it passes into the alkaline environment of the small bowel it becomes unionized and, therefore, available for systemic absorption. However, this is unlikely to raise systemic levels significantly due to a rapid hepatic first-pass metabolism, where it is N-demethylated to norfentanyl, which along with fentanyl is further hydroxylated. These inactive metabolites are excreted in the urine.

Alfentanil

Alfentanil is a synthetic phenylpiperidine derivative. It is a µ agonist but with some significant differences from fentanyl.

Presentation and Uses

Alfentanil is presented as a colourless solution containing 500 µg or 5 mg ml1. For short-term analgesia it is used in boluses of 525 µg.kg1. It is also used by infusion for sedation where its duration of action is significantly prolonged.

Kinetics

Alfentanil has a pKa = 6.5; at a pH of 7.4, 89% is present in the unionized form and is, therefore, available to cross lipid membranes. Fentanyl has a pKa = 8.4, so only 9% is unionized at a pH of 7.4. So despite a significantly lower lipid solubility than fentanyl it has a faster onset of action (when given in equipotent doses). Alfentanil has a much smaller initial volume of distribution so that despite a smaller clearance its elimination half-life is also shorter.

Metabolism occurs in the liver by N-demethylation to noralfentanil. This and other metabolites are conjugated and excreted in the urine. Midazolam is metabolized by the same hepatic enzymes (CYP3A3/4) and so when given together both elimination half-lives are significantly increased. Erythromycin may prolong alfentanil's activity by inhibiting cytochrome P450.

Remifentanil

The pure μ agonist remifentanil is a synthetic phenylpiperidine derivative of fentanyl with a similar potency. While it shares many of the effects associated with the opioids its metabolism makes it unique in this class of drug. It is not a controlled drug.

Presentation

Remifentanil is presented as a crystalline white powder in glass vials containing 1, 2 or 5 mg remifentanil hydrochloride. The preparation also contains glycine and is not licensed for spinal or epidural administration.

Uses

Remifentanil is administered intravenously by infusion. It should be diluted before use with 5% dextrose, 0.9 or 0.45% saline, in which it is stable for 24 hours. It is not recommended for use as a sole induction agent and is given as an initial bolus of 1 μg.kg1 over not less than 30 seconds, followed by an infusion that will vary according to the choice of supplemental anaesthesia. The usual dose range is 0.052.00 μg.kg1.min1.

While it is capable of producing intense analgesia during administration it should be remembered that additional post-operative analgesia is required following painful procedures due to its short duration of action.

Table 9.2: Various pharmacological properties of some opioids.

	Elimination half-life (min)	Clearance (ml.kg1.min1)	Volume of distribution (l.kg1)	Plasma protein-bound (%)	pKa	Percentage unionized (at pH 7.4)	Relative lipid solubility (from octanol: water coefficient)
Morphine	170	16	3.5	35	8.0	23	1
Pethidine	210	12	4.0	60	8.7	5	30
Fentanyl	190	13	4.0	83	8.4	9	600
Alfentanil	100	6	0.6	90	6.5	89	90
Remifentanil	10	40	0.3	70	7.1	68	20

Effects

Remifentanil shares many of morphine's effects including respiratory depression and chest wall rigidity. However, due to its ultra-short duration of action nausea and vomiting seem to be less common. It characteristically causes a fall in heart rate and blood pressure, which may be reversed by glycopyrrolate. Its analgesic effects are reversed by naloxone.

Kinetics

Remifentanil is rapidly broken down by non-specific plasma and tissue esterases resulting in an elimination half-life of 310 minutes. Its duration of action is, therefore, determined by metabolism and not distribution (cf. alfentanil and fentanyl). Owing to the abundance of these esterases the duration of administration does not effect the elimination half-life, i.e. the context sensitive half-time does not change (cf p57). This is in contrast to the other opioids whose half-time is context sensitive, being dependent on the duration of infusion. It is a poor substrate for plasma cholinesterases and as such is unaffected by cholinesterase deficiency. Anticholinesterase drugs do not alter its metabolism. An essentially inactive carboxylic acid metabolite (1/4600th as potent) is excreted in the urine. The half-life of this metabolite in the healthy adult is 2 hours. Impaired hepatic and renal function do not prolong its effects.

Tramadol

Tramadol is a cyclohexanol derivative. It is a racemic mixture, each enantiomer producing specific actions.

Presentation

Tramadol is available as 50 mg tablets and as a solution for intravenous or intramuscular injection containing 100 mg in 2 ml. Its analgesic potency is one-fifth to one-tenth that of morphine.

Mechanism of Action

Tramadol has agonist properties at all opioid receptors but particularly at μ receptors but has not been classified as a controlled drug. It also inhibits the re-uptake of noradrenaline and 5-HT, and stimulates presynaptic 5-HT release, which provides an alternative pathway for analgesia involving the descending inhibitory pathways within the spinal cord.

Effects

In equi-analgesic doses to morphine, tramadol produces less respiratory depression and constipation. In other respects it has similar actions to morphine. Respiratory depression and analgesia are reversed by naloxone.

Interactions

When administered with carbamazepine its serum concentrations are reduced resulting in diminished analgesia. It also has the potential to interact with drugs that inhibit central 5-HT or noradrenaline re-uptake, i.e. the tricyclic antidepressants and selective serotonin re-uptake inhibitors, resulting in seizures. It should not be used in patients with epilepsy.

Kinetics

Tramadol is well absorbed from the gut with an oral bioavailability of 70% which increases to more than 90% after repeated doses. It is metabolized in the liver by demethylation and subsequent glucuronidation to a number of metabolites, only one of which (O-desmethyltramadol) has been shown to have analgesic activity. These products are excreted in the urine. Its volume of distribution is 4 l.kg1 and its elimination half-life is 56 hours.

Naloxone

Naloxone is a pure opioid antagonist and will reverse opioid effects at μ, k and d receptors, although its affinity is highest for μ receptors. It may, however, also cause hypertension, pulmonary oedema and cardiac arrhythmias. In addition it may also cause antanalgesic effects in opioid naive subjects.

At 14 μg.kg1 intravenously it is the drug of choice in opioid overdose. However, its duration of action at 3040 minutes is shorter than morphine and high-dose fentanyl so that supplementary doses or an infusion of naloxone may be required.

Opioid Partial Agonists

This group of drugs has been used to control pain and to reverse opioid-induced respiratory depression with variable success. They are not widely used.

Nalorphine was the first partial agonist to be introduced as a morphine antagonist but was subsequently found to have analgesic effects of its own. It produced a high incidence of psychomimetic effects at analgesic doses and is no longer available.

Pentazocine produces analgesia with little respiratory depression. However, side-effects including nausea, vomiting, hallucinations and dysphoria have meant that it is rarely used.

Buprenorphine is structurally similar to and more potent than morphine with a duration of up to 10 hours due to receptor binding. Increasing doses does not appear to increase respiratory depression and may even reverse it. Nausea and vomiting are severe and prolonged.

Nalbuphine is equipotent to morphine but appears to have a ceiling effect with respect to its respiratory depression. However, severe respiratory depression has

Table 9.3: Summary of actions of some partial agonists at various opioid receptors.

	Agonist action at:	Antagonist action at:
Nalorphine	s, k	μ
Pentazocine	s, k	μ
Buprenorphine	μ (partial)	
Nalbuphine	s (partial), k(partial)	μ

been reported although this is readily reversed with naloxone. Unfortunately increasing doses does not appear to increase its analgesic actions. It produces marked sedation.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are used widely to treat mild to moderate pain, and also to reduce opioid consumption in the peri-operative period. They are more effective against somatic pain.

The route of administration is usually oral or rectal although some agents may be administered intravenously (tenoxicam, ketorolac). Absorption is rapid through the small bowel. NSAIDs are highly protein-bound in the plasma and have low volumes of distribution. The effects of other highly protein-bound drugs (e.g. warfarin) may be potentiated as they become displaced. Characteristically these drugs are metabolized in the liver and excreted in an inactive form in the urine and bile.

Mechanism of Action

NSAIDs inhibit the enzyme cyclo-oxygenase thereby preventing the production of both prostaglandins and thromboxanes from membrane phospholipids (Figure 9.3). Aspirin produces irreversible inhibition by enzyme acetylation, so that prostaglandin and thromboxane production become dependent on the synthesis of new cyclo-oxygenase. The other NSAIDs produce reversible enzyme inhibition, the activity of cyclo-oxygenase resuming when plasma NSAID levels fall. Decreased PGE2 and PGF2a synthesis account for their anti-inflammatory effect, while reduced thromboxane synthesis leads to reduced platelet aggregation and adhesiveness. Their antipyretic actions are due to inhibition of centrally produced prostaglandins that stimulate pyrexia. Reduced prostaglandin synthesis in gastric mucosal cells may lead to mucosal ulceration. Lipoxygenase is not inhibited by NSAIDs and the production of leukotrienes is unaltered.

Cyclo-oxygenase (COX) exists as two isoenzymes, COX1 and COX2. COX1 (the constitutive form) is responsible for the production of prostaglandins that

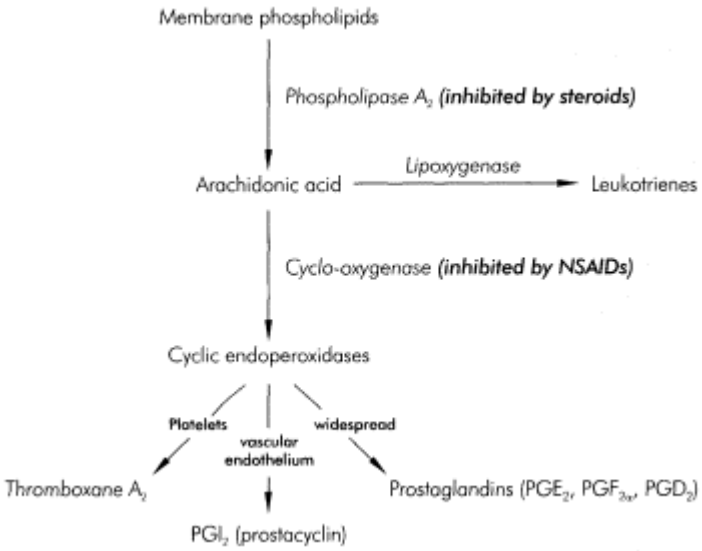


Figure 9.3:
Prostaglandin synthesis.

control renal blood flow, haemostatic function and form the protective gastric mucosal barrier. COX2 (the inducible form) is produced in response to tissue damage and facilitates the inflammatory response. Inhibition of COX1 appears to be responsible for the side-effects of NSAIDs while inhibition of COX2 provides anti-inflammatory, analgesic and antipyretic effects. This simplistic division may obscure a more complex physiological reality as COX2 is also involved in the production of protective prostaglandins in the presence of *H. pylori*-induced gastritis. NSAIDs have other effects that often limit their use.

Other Effects

• Gastric irritationintestinal erosions not limited to the stomach are commonly encountered during prolonged administration of NSAIDs and may cause iron deficiency anaemia. Many elements (mucous layer, bicarbonate secretion, rapid cell turnover and an abundant blood supply) are involved in the protection of the intestinal mucosa against acid and enzyme attack. Prostaglandins are involved in many of these elements so that when their synthesis is inhibited, protection is reduced. During aspirin therapy acetylsalicylate and salicylate ions are trapped in the alkaline environment of the mucosal cells thereby increasing their potential for side-effects. The potential for haemorrhage is increased due to its effect on platelet function. Meloxicam is more selective towards COX2 and has been associated with reduced gastric ulceration although a similar renal toxicity profile when compared with other

NSAIDs. Diclofenac blocks both forms equally while indomethacin and aspirin have a much higher affinity for COX1.

• NSAID sensitive asthmaacute severe asthma may be precipitated in up to 20% of asthmatics when given NSAIDs, and is associated with chronic rhinitis or nasal polyps. Those affected are usually middle-agedchildren are relatively spared. By inhibiting cyclo-oxygenase more arachidonic acid is converted to leukotrienes which are known to cause bronchospasm. Aspirin also causes an abnormal reaction to the platelets of susceptible patients causing the release of cytotoxic mediators.

• Renal functionrenally produced prostaglanclins (PGE2 and PGI2) are essential in maintaining adequate renal perfusion when the level of circulating vasoconstrictors (renin, angiotensin, noradrenaline) is high. Aspirin and other NSAIDs may alter this delicate balance by inhibiting their production, reducing renal perfusion and potentially leading to acute renal failure. NSAIDs may precipitate fluid retention and this may become significant in those with heart failure. At low doses of aspirin (< 2 g.day1) urate is retained as its tubular secretion is inhibited. At higher doses (> 5 g.day1) aspirin becomes uricosuric as reabsorption of urates is inhibited to a greater degree. It is rarely used for this purpose as the side-effects at higher doses are unacceptable. Analgesic nephropathy may develop after prolonged use of aspirin. The features are papillary necrosis and interstitial fibrosis.

• Platelet functionwhile altered platelet function may be advantageous in certain circumstances (acute myocardial infarction and prevention of stroke), during the peri-operative period it may cause increased blood loss. The reduced production of cyclic endoperoxidases and thromboxane A2 prevents platelet aggregation and vasoconstriction and, therefore, inhibits the haemostatic process. The effects of aspirin on platelets last for the life span of the platelet for two reasons: platelets are unable to generate new cyclo-oxygenase and the enzyme inhibition is irreversible. Up to 14 days are required to generate new platelets.

• Drug interactionscaution should be exercised when NSAIDs are administered with anticoagulants such as heparin or warfarin especially as the latter may be displaced from its plasma protein-binding sites, increasing its effects. Serum lithium may be increased when administered with NSAIDs and its levels should, therefore, be monitored.

• Hepatotoxicitythis is normally observed following prolonged or excessive use of NSAIDs. Up to 15% of patients may experience a rise in serum transaminase levels, even following short courses.

Table 9.4: Classification of NSAIDs.

Group	Class	Drug
Non-specific COX inhibitors	salicylates	aspirin
	acetic acid derivatives	diclofenac, ketorolac, indomethacin
	anthralinic acids	mefanamic acid
	pyrazolones	phenylbutazone
	proprionic acids	ibuprofen, naproxen
	para-aminophenols	paracetamol
	oxicams	tenoxicam, piroxicam
Preferential COX2 inhibitors	oxicams	meloxicam
Specific COX2 inhibitors	pyrazole	celecoxib, rofecoxib

Non-Specific Cox Inhibitors

Salicylates:
Aspirin

Uses

Aspirin (acetylsalicylic acid) is widely used for its analgesic and anti-inflammatory effects. It is also used for its effects on platelet function in acute myocardial infarction and the prevention of stroke.

Mechanism of Action (see above)

At low dose aspirin selectively inhibits platelet cyclo-oxygenase while preserving vessel wall cyclo-oxygenase. This has the effect of reducing TXA2-induced vasoconstriction and platelet aggregation, while leaving vessel wall synthesis of prostaglandins unaltered and, therefore, dilated.

Other Effects

• Metabolicaspirin also has effects on the metabolic state, which are usually of little significance but in overdose these become significant. It uncouples oxidative phosphorylation, thereby increasing oxygen consumption and carbon dioxide production. Initially minute ventilation is increased to keep PaCO2 static. However, when aspirin levels are increased significantly the respiratory centre is stimulated directly causing a respiratory alkalosis. The picture is complicated in the premorbid state by a metabolic acidosis. However, in children the respiratory centre is depressed by rising aspirin levels, and a metabolic acidosis occurs earlier so that a mixed respiratory and metabolic acidosis is more common.

Features of Aspirin Overdose

Common

- usually consciousonly unconscious in massive overdose
- sweaty
- tinnitus
- blurred vision
- tachycardia
- pyrexia
- hyperventilation
- respiratory alkalosis (subsequently complicated by metabolic acidosis)

Rare

- nausea and vomiting, epigastric pain
- oliguria
- gastrointestinal bleed
- pulmonary oedema (due to increased capillary permeability)
- coagulopathy
- hypokalaernia
- hypo- or hyperglycaemia
- encephalopathic, unconscious

Treatment

- gastric lavage and activated charcoal
- forced alkaline diuresis
- haemofiltration/haemodialysis

Reye's syndrome is uncommon and affects mainly children. Its aetiology has been linked to aspirin. It causes widespread mitochondrial damage, fatty changes in the liver progressing to hepatic failure, encephalopathy with cerebral oedema and has a mortality rate of up to 40%. Therefore, aspirin is only recommended for children below 12 years of age when specifically indicated, e.g. for juvenile arthritis (Still's disease).

Kinetics

Aspirin is a weak acid with a pKa = 3 and is present essentially in the unionized form in the stomach allowing gastric absorption, but due to the relatively alkaline nature of the mucosal cells salicylate ions may become trapped and unable to reach the systemic circulation. However, due to total surface area the small bowel

absorbs more drug. Once in the systemic circulation 85% is protein-bound, mainly by albumin. It is rapidly hydrolysed by intestinal and hepatic esterases to salicylate, which undergoes further hepatic metabolism to salicyluric acid and glucuronide derivatives. Salicylate and its metabolites are excreted in the urine (enhanced under alkaline conditions). The elimination half-life varies because glycine conjugation (converting salicylate to salicyluric acid) may become saturated in overdose resulting in zero-order kinetics.

Para-aminophenols:
Paracetamol

While paracetamol has essentially no effect on cyclo-oxygenase in vitro it has been classified as a NSAID because of its moderate analgesic and antipyretic properties. It has been proposed that its antipyretic actions are due to inhibition of prostaglandin synthesis within the central nervous system. However, its exact mechanism of action is unclear.

Presentation and Uses

Paracetamol is presented as 500 mg tablets alone and in combination with weak opioids. Suppositories contain 125 mg and 1 g and the paediatric elixir contains 120 mg in 5 ml. A preparation containing 100 mg methionine and 500 mg paracetamol is available, but at increased cost. The adult dose is 4 g.day1 in divided doses. The initial paediatric dose is 1530 mg.kg1 which is then reduced to 1015 mg.kg1 4 hourly with a maximum dose of 90 mg.kg1.day1.

Kinetics

Paracetamol is well absorbed from the small bowel and has an oral bioavailability of 80%. Unlike the other NSAIDs it does not cause gastric irritation, is less protein-bound (10%) and has a larger volume of distribution. Paracetamol is metabolized by the liver mainly to glucuronide conjugates, but also to sulphate and cysteine conjugates. These are actively excreted in the urine, only a small fraction

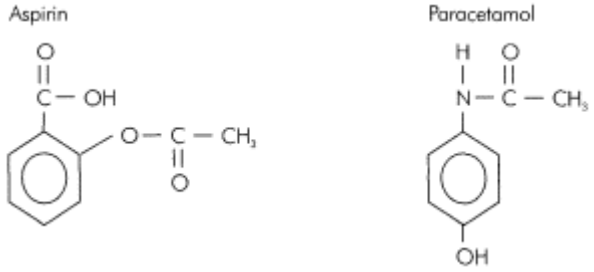


Figure 9.4:
Structures of aspirin and paracetamol.

being excreted unchanged. N-acetyl-p-amino-benzoquinoneimine is a highly toxic metabolite of paracetamol that is produced in small amounts following therapeutic doses. It is rapidly conjugated with hepatic glutathione to render it harmless.

Toxicity

Following a toxic dose the normal hepatic conjugation pathways become saturated so that more N-acetyl-p-amino-benzoquinoneimine is produced which rapidly exhausts hepatic glutathione. It then is free to form covalent bonds with sulphydryl groups on hepatocytes resulting in cell death and centrilobular hepatic necrosis. Treatment with oral methionine and oral or intravenous acetylcysteine is directed at replenishing hepatic glutathione. Methionine enhances glutathione synthesis while acetylcysteine is hydrolysed to cysteine, which is a glutathione precursor. Intravenous acetylcysteine is preferred as vomiting is common in paracetamol overdose.

Features of Paracetamol Overdose

- Normally remain conscious
- Nausea and vomiting
- Epigastric pain
- Sweating
- Erythema, urticaria, mucosal lesions
- Acute haemolytic anaemia
- Peripheral vasodilatation and shock following massive overdose
- Delayed hyperglycaemia
- Hepatic failure after 48 hours
    - LFT and clotting (INR) worst at 35 days
    - cholestasis
    - fulminant hepatic failure at 37 clays

Treatment

- Gastric lavage and activated charcoal
- Intravenous glucose
- Acetylcysteine or methionine
- Early referral to specialist centre

Acetic Acid Derivatives:
Diclofenac

Diclofenac is a phenylacetic acid derivative.

Presentation

Diclofenac is available in a parenteral as well as an oral and rectal formulation. The intravenous preparation should be diluted and administered over a minimum of 30 minutes. It is also available in combination with misoprostil, which provides prophylaxis against gastric and duodenal ulceration. The maximum adult dose is 150 mg.day1 in divided doses. The paediatric dose is 1 mg.kg1 tds for pain associated with minor surgery (tonsillectomy, inguinal herniotomy).

Uses

Diclofenac may be used alone to treat mild to moderate post-operative pain or to reduce opioid consumption when treating severe pain. It is particularly useful in treating renal colic. Owing to its effects on cyclo-oxygenase it may also precipitate gastric irritation, acute renal impairment and reduced platelet function which often prevents it from being used in major surgery.

Other Effects

- Gutdiclofenac produces less gastric irritation than both indomethacin and aspirin.

- Painthe parenteral formulation is highly irritant and intramuscular injection may be very painful and is associated with muscle damage. Intravenous injection causes thrombosis.

- Interactionsplasma concentrations of lithium and digoxin may be increased. In general it does not effect either oral anticoagulants or oral hypoglycaemic agents but isolated reports would suggest that close monitoring is used.

Kinetics

In keeping with other drugs in its class diclofenac is well absorbed from the gut, highly plasma protein-bound (99%), and has a small volume of distribution (0.15 l.kg1). It undergoes hepatic hydroxylation and conjugation to inactive metabolites that are excreted in the urine (60%) and bile (40%).

Ketorolac

Ketorolac is an acetic acid derivative with potent analgesic activity but limited anti-inflammatory activity. It is also a potent antipyretic. It may be given orally or parenterally and has a duration of action of up to 6 hours. It shares the side-effect

profile common to all NSAIDs. It is specifically contraindicated in patients on low-dose heparin despite work showing that any interaction is probably of no clinical significance.

Indomethacin

Indomethacin is a potent anti-inflammatory agent but is a less effective analgesic. Rectal use has been associated not only with a reduced peri-operative opioid requirement, but also with reduced platelet function resulting in wound haematoma and increased blood loss. It is used to promote closure of the ductus arteriosus in the premature infant by inhibiting prostaglandin synthesis. It shares the other effects common to NSAIDs but has been particularly linked with headache. It may also impair hepatic function and antagonize the effects of diuretics and angiotensin-converting enzyme inhibitors.

Kinetics

Indomethacin is well absorbed from the gut with an oral bioavailability of 80%. It is more than 99% bound by plasma proteins and is metabolized to inactive metabolites that are excreted in the urine and bile. Five percent is excreted unchanged.

Pyrazolones:
Phenylbutazone

Phenylbutazone is a potent anti-inflammatory agent. Its use has been limited to hospital patients with ankylosing spondylitis due to serious haematological side-effects including agranulocytosis and aplastic anaemia. It is significantly bound by plasma proteins and will interact with other highly bound drugs. It may also impair hepatic function, produce a rash, and cause sodium and water retention.

Proprionic Acids:
Ibuprofen

Ibuprofen is prepared as 200600 mg tablets and as a paediatric elixir containing 20 mg.ml1. It is not recommended for children below 1 year of age. The paediatric dose is 20 mg.kg1.day1 in divided doses. It has mild anti-inflammatory and analgesic effects but has the lowest incidence of side-effects of the most commonly used NSAIDs.

Oxicams:
Tenoxicam

Tenoxicam exhibits many of the features in common with other NSAIDs. Two specific features make it particularly useful in the peri-operative period.

- It may be given intravenously resulting in a rapid onset of action
- It has a long elimination half-life (72 hours) resulting in a long duration of action and allowing once daily dosage.

However, these advantages may become disadvantages if side-effects become significant.

Kinetics

Tenoxicam is well absorbed from the gut and has a high oral bioavailability. It is highly plasma protein-bound (99%). Clearance from the body is due to metabolism to an inactive metabolite that is excreted in the urine (66%) and in bile (33%). The dose is 20 mg.day1.

Preferential COX2 Inhibitors

Meloxicam

Presentation

Meloxicam is available as tablets and suppositories and the initial dose is 7.5 mg.day1, which may be doubled.

Meloxicam has limited preferential selectivity for COX2 and is quoted as being between 3 to 50 times as potent against COX2. At a dose of 7.5 mg.day1 it has a reduced gastrointestinal side-effect profile when compared with diclofenac, although its renal side-effect profile appears to be equivalent to other NSAIDs.

Kinetics

Meloxicam is slowly, but almost completely absorbed from the gut with an oral bioavailability of 90%. It is 99% protein-bound, essentially to albumin. Metabolism occurs in the liver to inactive metabolites that are excreted in the urine (50%) and bile (50%). Three percent is excreted unchanged in the urine. The elimination half-life is 20 hours.

Specific COX2 Inhibitors

Celecoxib

Celecoxib has recently been released in the USA and has a 375-fold selectivity for COX2 in certain assays. It has been shown to be effective for arthritis and have a gastrointestinal side-effect profile over 6 months equivalent to that of placebo and less than that of diclofenac.

Rofecoxib

Rofecoxib has recently been released in the UK and has at least an 800-fold selectivity for COX2.

Table 9.5: Clinical and kinetic data for some NSAIDs.

Drug	Maximum daily dose	Elimination half-life (h)	Plasma protein-binding (%)	Analgesic and antipyretic activity	Anti-inflammatory activity
Aspirin	4 g	variable*	85	+ + +	+ +
Paracetamol	4 g	2	10	+ + +	+ +
Diclofenac	150 mg	12	99	+	+ + +
Ketorolac	40 mg	5	99	+ +	+
Indomethacin	200 mg	6	95	+	+ + +
Phenylbutazone	300 mg	50100	98	+	+ + + +
Tenoxicam	20 mg	72	99	+	+ +
Meloxicam	15 mg	20	99	+	+ +
Ibuprofen	1.8 g	23	99	+	+

*When obeying first-order kinetics the t1/2 elimination of aspirin is short (1530 min.) However, this is significantly prolonged when enzyme systems become saturated and its kinetics become zero-order.

10
Local Anaesthetics

Physiology

Individual nerve fibres are made up of a central core (axoplasm) and a phospholipid membrane containing integral proteins, some of which function as ion channels.

The Resting Membrane Potential

The neuronal membrane contains the enzyme Na+/K+ ATPase that actively maintains a 30-fold K+ concentration gradient (greater concentration inside) and a 10-fold Na+ concentration gradient (greater concentration outside). As the neuronal membrane is permeable to K+ it tends to flow down its concentration gradient out of the cell. However, intracellular anionic proteins tend to oppose this ionic flux, and the balance of these processes results in the resting membrane potential of 80 mV (negative inside). It can, therefore, be seen that the ratio of intracellular to extracellular K+ alters the resting membrane potential. Hypokalaemia increases (makes more negative) the resting membrane potential while the Na+ concentration has little effect, as the membrane is essentially impermeable to Na+ when in the resting state.

The Action Potential

The action potential is generated by altered Na+ permeability across the phospholipid membrane and lasts only 12 milliseconds. Electrical or chemical triggers initially cause a slow rise in membrane potential until the threshold potential (about 50 mV) is reached. Voltage sensitive Na+ channels then open, increasing Na+ permeability dramatically and the membrane potential briefly reaches +30 mV (approaching the Na+ equilibrium potential of +67 mV) at which point the Na+ channels close. The membrane potential returns to its resting value with an increased efflux of K+. The Na+/K+ ATPase restores the concentration gradients although the total number of ions moving across the membrane is small. Conduction along unmyelinated fibres is relatively slow compared with myelinated fibres where current jumps from one node of Ranvier to another (saltatory conduction) and reaches 120 m.s1. Retrograde conduction is not possible under normal circumstances due to inactive Na+ channels following the action potential.

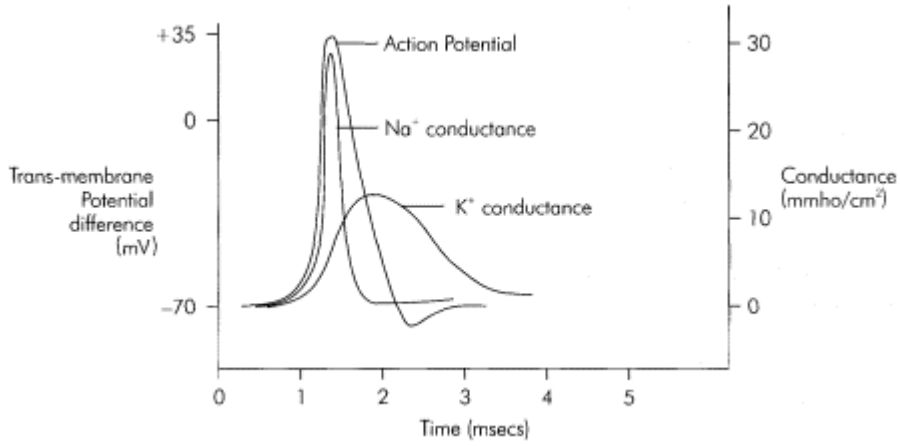


Figure 10.1:
Changes in Na+ and K+ conductance during the action potential.

Local Anaesthetics

Preparations

Local anaesthetics are formulated as the hydrochloride salt to render them watersoluble. They often contain the preservative sodium metabisulphite and a fungicide. Multidose bottles contain 1 mg.ml1 of the preservative methyl parahydroxybenzoate. Only the single-dose ampoules without additives (apart from glucose at 80 mg.ml1 used in 'heavy' bupivacaine) are suitable for subarachnoid administration as the preservatives carry the risk of precipitating arachnoiditis. Adrenaline or felypressin (a synthetic derivative of vasopressin with no antidiuretic effect) are added to some local anaesthetic solutions in an attempt to slow down absorption from the site of injection and to prolong the duration of action. Lignocaine is available in a large range of concentrations varying from 0.5 to 10%. The high concentrations are used as a spray to anaesthetize mucous membranes (note 1% = 10 mg.ml1).

Mechanism of Action

Local anaesthetic action is dependent on blockade of the Na+ channel. Unionized lipid soluble drug passes through the phospholipid membrane where, in the axoplasm it is protonated. In this ionized form it binds to the internal surface of a Na+ channel, preventing it from leaving the inactive state. The degree of blockade in vitro is proportional to the rate of stimulation due to the attraction of local anaesthetic to 'open' Na+ channels (Figure 10.2).

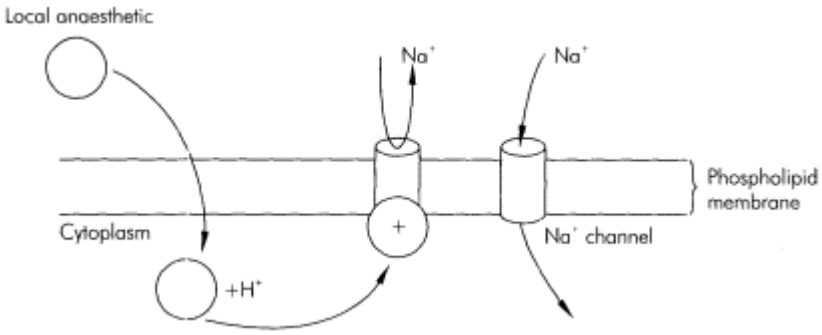


Figure 10.2:
Mechanism of action of local anaesthetics.

Alternatively 'membrane expansion' may offer an additional mechanism of action. Unionized drug dissolves into the phospholipid membrane and may cause swelling of the Na+ channel/lipoprotein matrix resulting in its inactivation.

Physiochemical Characteristics

Local anaesthetics are weak bases and exist predominantly in the ionized form at neutral pH as their pKa exceeds 7.4. They fall into one of two chemical groupings, ester or amide, which describes the linkage between the aromatic lipophilic group and the hydrophilic group that each group possesses. Esters are comparatively unstable in solution, unlike amides that have a shelf-life of up to 2 years (Table 10.1, Figure 10.3).

The individual structures confer different physiochemical and clinical characteristics.

• Potency is closely correlated to lipid solubility in vitro, but less so in vivo. Other factors such as vasodilator properties and tissue distribution determine the amount of local anaesthetic that is available at the nerve.

• The duration of action is closely associated with the extent of protein binding. Local anaesthetics with limited protein binding have a short

Table 10.1: Classification of local anaesthetics

Esters -CO.O-	Amides -NH.CO-
Procaine	Lignocaine
Amethocaine	Prilocaine
Cocaine	Bupivacaine
	Ropivacaine
	Dibucaine

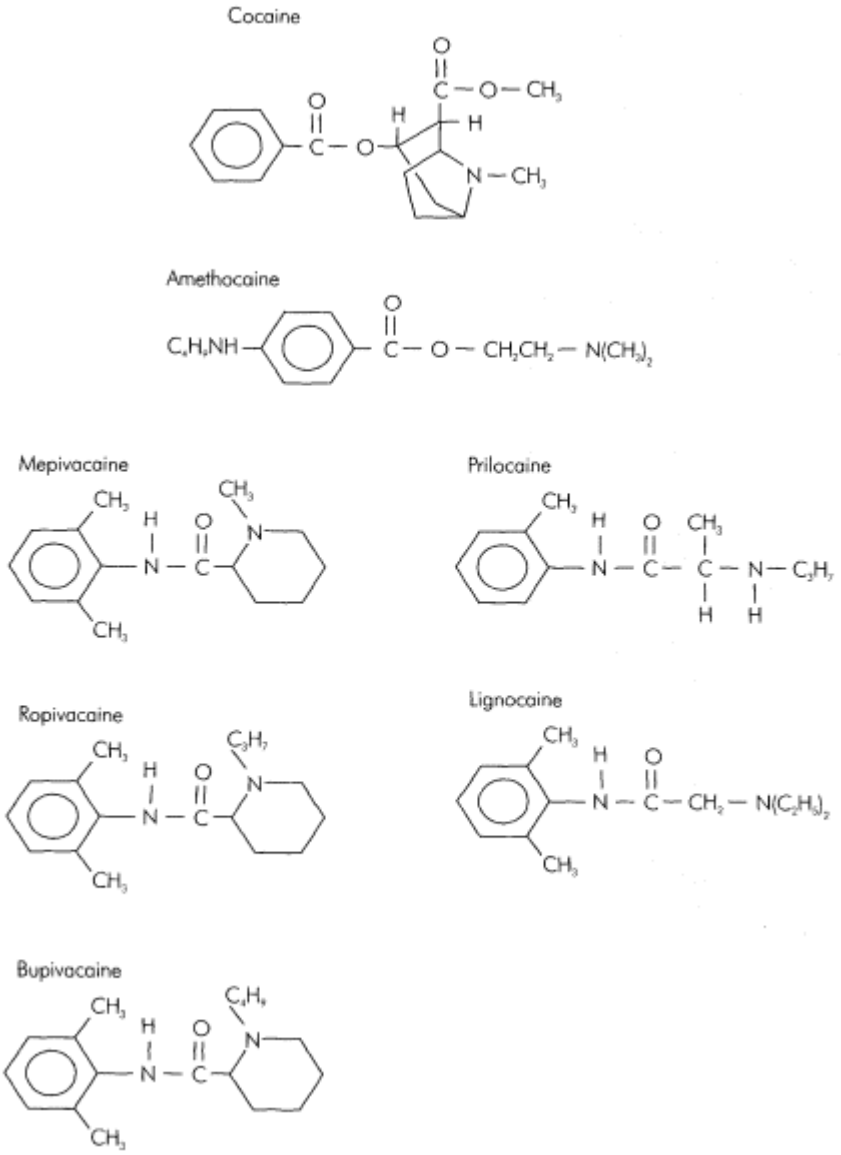


Figure 10.3:
Structure of some local anaesthetics.

duration of action, and conversely those with more extensive protein binding have a longer duration of action.

• The onset of action is closely related to pKa. Local anaesthetics are weak bases and exist mainly in the ionized form at normal pH. Those with a high pKa have a greater fraction present in the ionized form, which is unable to penetrate the phospholipid membrane, resulting in a slow onset of action. Conversely a low pKa reflects a higher fraction present in the unionized form and, therefore, a faster onset of action as more is available to cross the phospholipid membrane.

• The intrinsic vasodilator activity varies between drugs and influences potency and duration of action. In general, local anaesthetics cause vasodilatation in low concentration (prilocaine > lignocaine > bupivacaine > ropivacaine) and vasoconstriction at higher concentrations. However, cocaine has solely vasoconstrictor actions by inhibiting neuronal uptake of catecholamines (uptake 1) and inhibiting monoamine oxidase (MAO).

However, total dose and concentration of administered local anaesthetic will also have a significant effect on a given clinical situation.

Local anaesthetics are generally ineffective when used to anaesthetize infected tissue. The acidic environment further reduces the unionized fraction of drug available to diffuse into and block the nerve. There may also be increased local vascularity which increases removal of drug from the site.

Lignocaine: pKa = 7.9

At pH 7.4

$$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

$$7.4 = 7.9 + \log \frac{[B]}{[BH^+]}$$

$$-0.5 = \log \frac{[B]}{[BH^+]}$$

$$0.3 = \frac{[B]}{[BH^+]}$$

so 75% ionized and 25% unionized

at pH of 7.1

$$7.1 = 7.9 + \log \frac{[B]}{[BH^+]}$$

$$0.16 = \frac{[B]}{[BH^+]}$$

so 86% ionized and 14% unionized (i.e. less available to penetrate nerves)

Other Effects

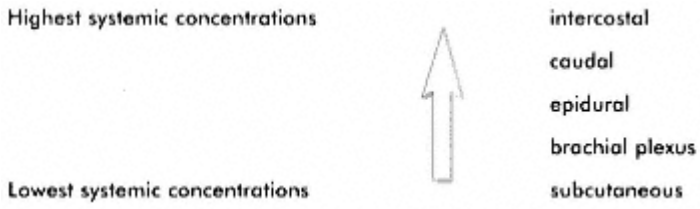
• Cardiaclignocaine is widely used to treat ventricular arrhythmias, while bupivacaine is not. Both drugs block cardiac Na+ channels and decrease the maximum rate of increase of phase 0 of the cardiac action potential (cf. chapter 14). They also have direct myocardial depressant properties (bupivacaine > lignocaine). The PR and QRS intervals are also increased and the refractory period prolonged. However, bupivacaine is much slower at dissociating from the Na+ channels resulting in persistent depression. This may lead to re-entrant arrhythmias and ventricular fibrillation. In addition, tachycardia may enhance frequencydependent blockade by bupivacaine, which adds to its cardiac toxicity. Life-threatening arrhythmias may also reflect disruption of Ca2+ and K+ channels. Ropivacaine differs from bupivacaine both in the substitution of a propyl for a butyl group and in its preparation as a single, S, enantiomer. It dissociates more rapidly from cardiac Na+ channels and produces less direct myocardial depression than bupivacaine, and is, therefore, less toxic. However, it has a slightly shorter duration of action and is slightly less potent than bupivacaine resulting in a slightly larger dose requirement for an equivalent block.

• Central nervous systemlocal anaesthetics penetrate the brain rapidly and have a bi-phasic effect. Initially inhibitory interneurones are blocked resulting in excitatory phenomenoncircumoral tingling, visual disturbance, tremors and dizziness. This is followed by convulsions. Finally, all central neurones are depressed leading to coma and apnoea.

Kinetics

Absorption

The absorption of local anaesthetics into the systemic circulation varies depending on the characteristics of the agent used, the presence of added vasoconstrictor and the site of injection.



Clearly if local anaesthetic is inadvertently injected into a vein or artery very high systemic levels will result and possibly cause central nervous system or cardiovascular toxicity. Less than 10 mg lignocaine inadvertently injected into the carotid or vertebral artery will result in a rapid rise in central nervous system concentrations and will cause coma and possibly apnoea and cardiac arrest.

Distribution

Ester local anaesthetics are minimally bound while amides are more extensively bound (bupivacaine > ropivacaine > lignocaine > prilocaine) in the plasma. a1-acid glycoprotein binds local anaesthetic with high affinity although albumin binds a greater quantity due to its relative abundance. When protein binding is increased (pregnancy, myocardial infarction, renal failure, post-operatively and in infancy) the free fraction of drug is reduced.

The degree of protein binding will affect the degree of placental transfer. Bupivacaine is more highly bound than lignocaine, so less crosses the placenta. If the foetus becomes acidotic there will be an increase in the ionized fraction and local anaesthetic will accumulate in the foetus (ion trapping). Ester local anaesthetics do not cross the placenta in significant amounts due to their rapid metabolism.

Metabolism and Elimination

Esters are hydrolysed rapidly by plasma cholinesterases and other esterases to inactive compounds. Para-aminobenzoate is one of the main metabolites and has been associated with hypersensitivity reactions especially in the atopic patient. This rapid hydrolysis results in a short elimination half-life. Cocaine is the exception, undergoing hepatic hydrolysis to water-soluble metabolites that are excreted in the urine.

Amides undergo hepatic metabolism by amidases. Amidase metabolism is much slower than plasma hydrolysis and so amides are more prone to accumulation when administered by continuous infusion. Reduced hepatic blood flow or hepatic dysfunction can decrease amide metabolism.

Toxic Doses

Raised systemic blood levels of local anaesthetic lead initially to central nervous system and then to cardiovascular toxicity. However, the absorption of local anaesthetic varies widely depending on the site of administration and presence of vasoconstrictors. Therefore, the concept of a toxic dose without regard to the site of administration is meaningless. The toxic plasma levels are given in Table 10.2.

Intravenous Regional Anaesthesia

Bupivacaine has been used for intravenous regional techniques, but following a number of deaths attributed to cardiac toxicity it is no longer used for this purpose.

Table 10.2: Some pharmacological properties of various local anaesthetics.

	Relative potency	Onset	Duration of action	Toxic plasma Concentration (µg.ml1)	pKa	Percentage unionized (at pH 7.4)	Plasma protein-bound (%)	Relative lipid solubility	Elimination half-life (min)
Procaine	1	slow	short		8.9	3	6	1	
Amethocaine	8	slow	long		8.5	7	75	200	
Lignocaine	2	fast	moderate	> 5	7.9	25	70	150	100
Prilocaine	2	fast	moderate	> 5	7.7	33	55	50	100
Bupivacaine	8	moderate	long	> 1.5	8.1	15	95	1000	160
Ropivacaine	8	moderate	long	> 4	8.1	15	94	300	120
Mepivacaine	2	slow	moderate	> 5	7.6	40	77	50	115

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Prilocaine (0.5%) is commonly used in this setting although lignocaine may also be used.

Lignocaine

Lignocaine is an amide local anaesthetic that is also used to control ventricular tachyarrhythmias. It has Class Ib anti-arrhythmic actions (see Chapter 14).

Preparations

Lignocaine is formulated as the hydrochloride and is presented as a colourless solution (0.52%) with or without adrenaline (1 in 80200 000); a 2% gel; a 5% ointment; a spray delivering 10 mg.dose1 and a 4% solution for topical use on mucous membranes. It is also combined in suppository form with steroid for use in haemorrhoids.

Kinetics

Lignocaine is 70% protein-bound to a1-acid glycoprotein. It is extensively metabolized in the liver by dealkylation to monoethylglycine-xylidide and acetaldehyde. The former is further hydrolysed while the latter is hydroxylated to 4-hydroxy2,6-xylidine forming the main metabolite, which is excreted in the urine. Some of the metabolic products of lignocaine have anti-arrhythmic properties while others may potentiate lignocaine-induced seizures.

Clearance is reduced in the presence of hepatic or cardiac failure.

Eutectic Mixture of Local Anaesthetic (EMLA)

When two compounds are mixed to produce a substance that behaves with a single set of physical characteristics, it is said to be eutectic. EMLA (5%) contains a mixture of crystalline bases of 2.5% lignocaine and 2.5% prilocaine in a white oil:water emulsion. The mixture has a lower melting point, being an oil at room temperature, while the individual components would be crystalline solids.

Presentation and Uses

EMLA is presented as an emulsion in tubes containing 5 or 30 g. It is used to anaesthetize skin before vascular cannulation or harvesting for skin grafts. It should be applied to intact skin under an occlusive dressing for at least 60 minutes to ensure adequate anaesthesia.

Cautions

EMLA cream should be avoided in patients with congenital or idiopathic methaemoglobinaemia, or in infants less than 12 months of age who are receiving treatment with methaemoglobin-inducing drugs. Patients taking drugs associated with methaemoglobinaemia (e.g. sulphonamides or phenytoin) are at greater risk

of developing methaemoglobinaemia if concurrently treated with EMLA cream. Methaemoglobinaemia is caused by o-toluidine, a metabolite of prilocaine.

EMLA should not be used on mucous membranes due to rapid systemic absorption. EMLA should also be used with caution in patients receiving Class I anti-arrhythmic drugs (e.g. tocainide, mexiletine) because the toxic effects are additive and potentially synergistic.

Bupivacaine

Presentation and Uses

Bupivacaine is prepared as a 0.25, 0.5 (with or without 1:200 000 adrenaline) and 0.75% solution. A 0.5% preparation containing 80 mg.ml1 glucose (specific gravity 1.026) is available for subarachnoid block.

While it has been the mainstay of epidural infusions in labour and post-operatively, concerns regarding its cardiac toxicity and the availability of ropivacaine may lead to reduced use.

Kinetics

The onset of action is intermediate or slow and significantly slower than that of lignocaine. It is the most highly protein-bound amide local anaesthetic and is metabolized in the liver by dealkylation to pipecolic acid and pipecolylxylidine.

Ropivacaine

Presentation and Uses

The amide local anaesthetic ropivacaine is prepared in three concentrations (2, 7.5 and 10 mg.ml1), in two volumes (10 and 100 ml) and as the pure S-enantiomer. It is not prepared in combination with a vasoconstrictor as this does not alter its duration of action or uptake from tissues. The R-enantiomer is less potent and more toxic. It has a propyl group on its piperidine nitrogen in contrast to the butyl group present in bupivacaine and the methyl group present in mepivacaine (Figure 10.3).

The main differences from bupivacaine lie in its pure enantiomeric formulation, improved toxic profile and lower lipid solubility. Its lower lipid solubility may result in reduced penetration of the large myelinated Aa motor fibres, so that initially these fibres are relatively spared from local anaesthetic. However, during continuous infusion they too will become blocked by local anaesthetic so that little difference remains between the large myelinated Aa fibres and the smaller unmyelinated C fibres, which are blocked rapidly. Therefore, the motor block produced by ropivacaine is slower in onset, less dense and of shorter duration when compared with an equivalent dose of bupivacaine. It would appear more

appropriate than bupivacaine for epidural infusion due to its sensory/motor discrimination and greater clearance.

Kinetics

Ropivacaine is metabolized in the liver by aromatic hydroxylation, mainly to 3-hydroxy-ropivacaine, but also to 4-hydroxy-ropivacaine, both of which have some local anaesthetic activity.

Prilocaine

Presentation and Uses

Prilocaine is presented as a 0.52.0% solution. It is also available as a 3% solution with felypressin (0.03 unit.ml1) for dental use. It has similar indications to lignocaine but is most frequently used for intravenous regional anaesthesia.

Kinetics

Prilocaine is the most rapidly metabolized amide local anaesthetic, metabolism occurring not only in the liver, but also the kidney and lung. When given in large doses one of its metabolites, o-toluidine, may precipitate methaemoglobinaemia. This may require treatment with ascorbic acid or methylene blue, which act as reducing agents. The neonate is at special risk as its red blood cells are deficient in methaemoglobin reductase. EMLA cream may precipitate the same reaction.

Cocaine

Presentation and Uses

Cocaine is an ester local anaesthetic derived from the leaves of *Erythroxylon coca*, a plant indigenous to Bolivia and Peru. It is used for topical anaesthesia and local vasoconstriction. Moffatt's solution (2 ml 8% cocaine, 2 ml 1% sodium bicarbonate, 1 ml 1:1000 adrenaline) has been used in the nasal cavities, although its potential for side-effects has rendered it less popular. Cocaine is also formulated as a paste ranging from 1 to 4%.

Mechanism of Action

Cocaine blocks uptake 1 and MAO while also stimulating the central nervous system. These combined effects increase the likelihood of precipitating hypertension and arrhythmias. Its use also provokes hyperthermia.

Side-Effects

When taken or administered in high doses it can cause confusion, hallucinations, seizures, arrhythmias and cardiac rupture.

Kinetics

Cocaine is absorbed well from mucous membranes and is highly protein-bound (about 98%). Unlike other esters it undergoes significant hepatic hydrolysis to inactive products which are excreted in the urine.

Amethocaine

Amethocaine is an ester local anaesthetic used for topical anaesthesia. It is presented as 0.5 and 1% drops for topical use before local anaesthetic block or as a sole agent for lens surgery. It may produce a burning sensation on initial instillation. It is also available as a 4% cream for topical anaesthesia to the skin and is used in a similar fashion to EMLA cream. However, it has a faster onset of action, producing good topical anaesthesia by 30 minutes, following which it may be removed. Its effects last for 46 hours. It produces some local vasodilatation and erythema that may assist venous cannulation.

11
Muscle Relaxants and Anticholinesterases

Physiology

The neuromuscular junction (NMJ) forms a chemical bridge between the motor neurone and skeletal muscle. The final short section of the motor nerve is unmyelinated and comes to lie in a gutter on the surface of the muscle fibre at its mid-pointeach being innervated by a single axonal terminal from a fast Aa neurone (*en plaque* appearance). However, for the intra-occular, intrinsic laryngeal and some facial muscles the pattern of innervation is different with multiple terminals from slower Ag neurones scattered over the muscle surface (*en grappe* appearance). Here, muscle contraction depends on a wave of impulses throughout the terminals.

The post-synaptic membrane has many folds; the shoulders contain acetylcholine (ACh) receptors while the clefts contain the enzyme acetylcholinesterase (AChE), which is responsible for the hydrolysis of ACh (Figure 11.1).

Acetylcholine

Synthesis

The synthesis of ACh (Figure 11.2) is dependent on acetyl-coenzyme A and choline, which is derived from the diet and recycled from the breakdown of ACh. Once synthesized in the axoplasm it is transferred into small synaptic vesicles where it is stored prior to release.

Release

When an action potential arrives at a nerve terminal it triggers Ca2+ influx, which then combines with various proteins to trigger the release of vesicular ACh. About 200 such vesicles (each containing about 10 000 molecules ACh) are released in response to each action potential.

Acetylcholine Receptor

Nicotinic ACh receptors are in groups on the edges of the junctional folds on the post-synaptic membrane. They are integral membrane proteins with a molecular

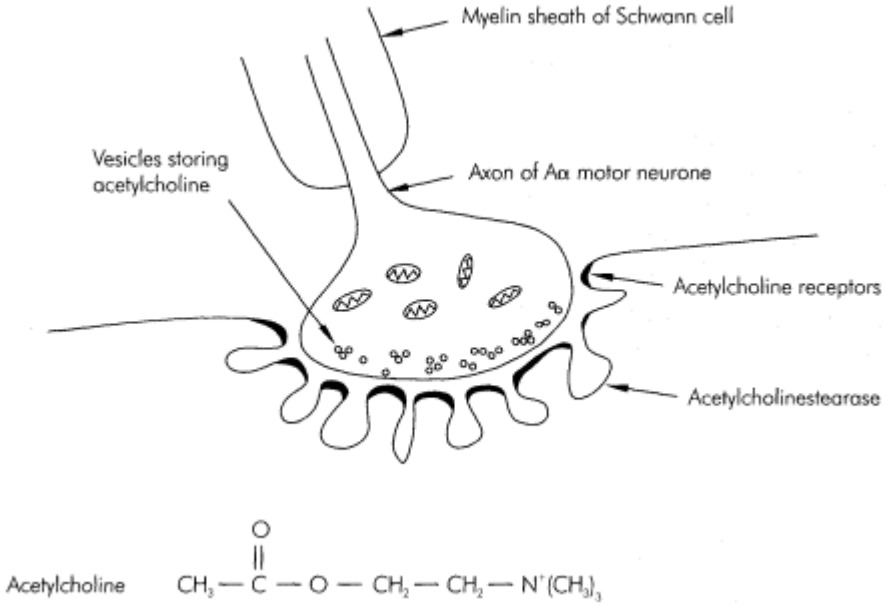


Figure 11.1:
Neuromuscular junction and structure of acetylcholine.

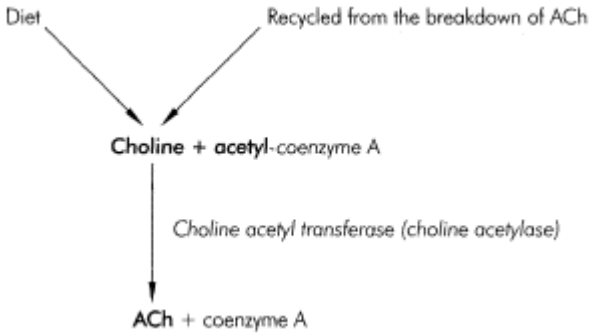


Figure 11.2:
Synthesis of acetylcholine (ACh).

weight of 250 000 Da and consist of five subunits (two a, and a single b, e and d in adults). They are configured with a central ion channel that opens when the a subunits (each of 40 000 Da) bind ACh. Binding the initial molecule of ACh increases the affinity of the second a subunit for ACh. These receptors are also present on the prejunctional membrane and provide positive feedback to maintain transmitter release during periods of high activity. When blocked by non-depolarizing muscle relaxants they may be responsible for 'fade' (Figure 11.3).

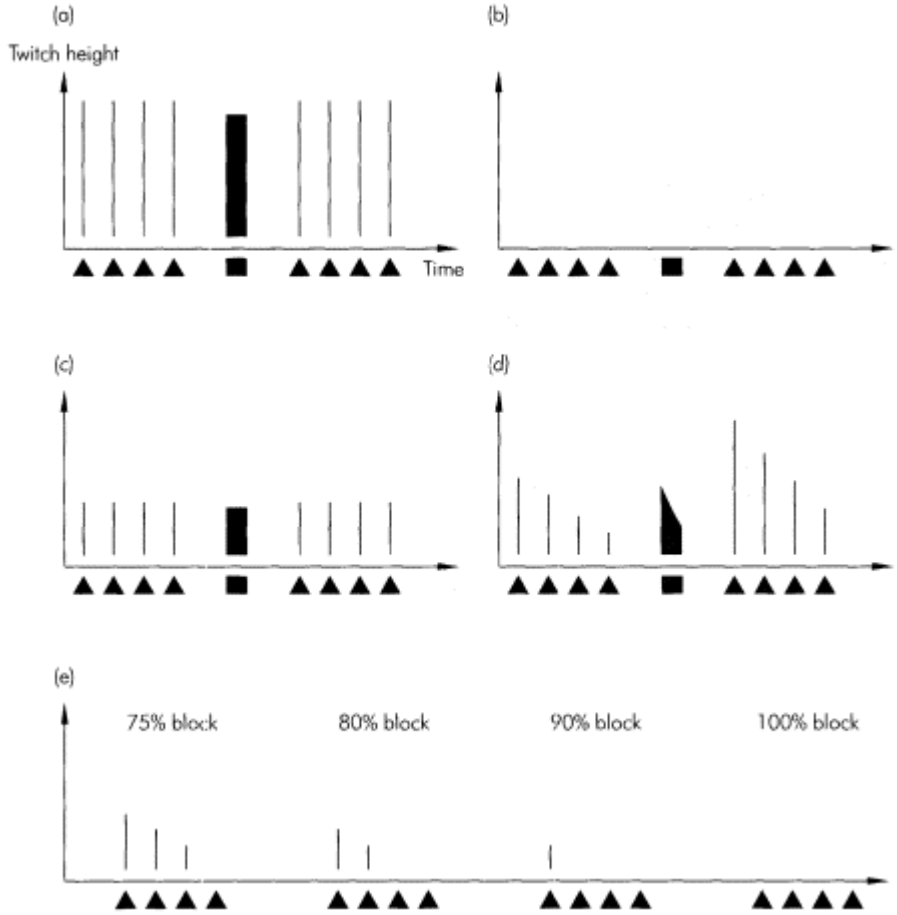


Figure 11.3:
Types of neuromuscular block. (a) Control, no muscle relaxant present; (b) complete block, either depolarizing or non-depolarizing; (c) partial depolarizing block, reduced but equal twitch height, no post-tetanic facilitation; (d) partial non-depolarizing block, reducing twitch height, fade on tetanic stimulation, post-tetanic facilitation; (e) the train of four reveals varying degrees of partial non-depolarizing block, count of 3 = 75% block, count of 2 = 80% block, count of 1 = 90% block, no count = 100% block. ▲, A single stimulus; ■, a 50 Hz tetanic stimulus).

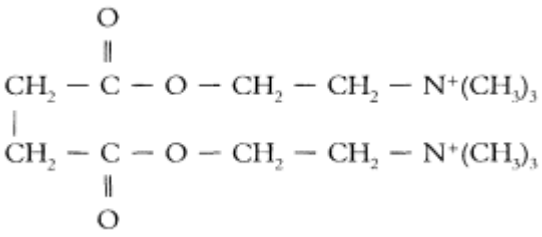
The ACh receptor ion channel is non-specific, allowing Na+, K+ and Ca2+ across the membrane, generating a miniature end-plate potential. These summate until the threshold potential is reached at which point voltage-gated Na+ channels are opened, causing a rapid depolarization, leading to the propagation of an action potential across the muscle surface. On reaching the T tubular system, Ca2+ is released from the sarcoplasmic reticulum which initiates muscle contraction.

Metabolism

ACh is metabolized by AChE, which is located on the junctional clefts of the postsynaptic membrane. AChE has an anionic and an esteratic binding site. The anionic site binds with the positively charged quaternary ammonium moiety, while the esteratic site binds the ester group of ACh. At the point of ACh breakdown choline is released and AChE becomes acetylated. The acetylated enzyme is rapidly hydrolysed and acetic acid is produced.

Depolarizing Muscle Relaxants

Suxamethonium



Suxamethonium was first introduced in 1952 and provided a significant advantage over tubocurarine as profound muscle relaxation of short duration was achieved rapidly. It can be thought of as two molecules of ACh joined back to back through their acetyl groups.

Presentation and Uses

Suxamethonium is formulated as a colourless solution containing 50 mg.ml1 and should be stored at 4°C. It is used to achieve rapid muscle relaxation required during rapid sequence induction and has also been used by infusion to facilitate short surgical procedures.

Mechanism of Action

Suxamethonium mimics the action of ACh by attaching to the nicotinic ACh receptor and causing membrane depolarization. However, because its hydrolysing enzyme (plasma or pseudo-cholinesterase) is not present at the NMJ its duration

of action is longer than that of ACh. The persistent depolarization produced initiates local current circuits that render the voltage sensitive Na+ channels within 12 mm inactive. This area of electrical inexcitability prevents the transmission of further action potentials resulting in muscle relaxation.

Initially this depolarizing block is described as a Phase I block; however, if further doses of suxamethonium are given it may become a Phase II block. The characteristics of a Phase II block are similar to those of a non-depolarizing block, but the mechanism is thought to be different (probably a pre-synaptic effect) (Table 11.1, Figure 11.3).

Kinetics

Suxamethonium is rapidly hydrolysed by plasma or pseudo-cholinesterase (an enzyme of the liver and plasmanone being present at the NMJ), to such an extent that only 20% of the initial intravenous dose reaches the NMJ, so that the rate of hydrolysis becomes a critical factor in determining the duration of the neuromuscular block. Suxamethonium is hydrolysed to choline and succinylmonocholine, which is weakly active. Succinylmonocholine is metabolized further by plasma cholinesterase to succinic acid and choline. Because metabolism is rapid, less than 10% is excreted in the urine (Figure 11.4).

Table 11.1: Characteristics of partial neuromuscular blockade.

	Partial depolarizing or Phase I block	Partial non-depolarizing or Phase II block
Single twitch	reduced	reduced
Train-of-four ratio (T4:T1)	> 0.7	< 0.7
1 Hz stimulus	sustained	fade
Post-tetanic potentiation	no	yes
Effect of anticholinesterases	block augmented	block antagonized

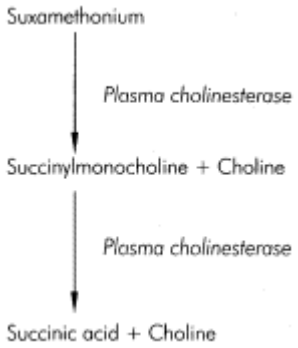


Figure 11.4:
Metabolism of suxamethonium.

Other Effects

Apart from its useful effects at the NMJ suxamethonium has many other effects all of which are detrimental:

• Arrhythmiassinus or nodal bradycardia, and ventricular arrhythmias can occur following suxamethonium, via stimulation of the muscarinic receptors in the sinus node. The bradycardia is often more severe after a second dose but may be prevented by atropine. This phenomenon is often more pronounced in children.

• Hyperkalaemiaa small rise in serum K+ is expected following suxamethonium in the normal subject as depolarization involves K+ efflux into extracellular fluid. Patients with burns (of > 10%) and neuromuscular disorders are susceptible to a sudden release of K+, which may be large enough to provoke cardiac arrest. Burns patients are at risk from about 24 hours after injury and for up to 18 months. Extra-junctional ACh receptors (which contain a foetal g subunit in place of an adult e subunit) proliferate over the surface of the muscle, and when activated release K+ into the circulation. Patients with paraplegia, progressive muscle disease or trauma-induced immobility are at risk via a similar mechanism. The period of particular risk in those with paraplegia is during the first 6 months but it continues in those with progressive muscle disease, becoming more severe as more muscle is involved.

Those with renal failure are not at increased risk of a sudden hyperkalaemic response to suxamethonium *per se.* However, serum K+ may be grossly deranged in acute renal failure leading to an increased risk of arrhythmias.

• Myalgiamuscle pains are commonest in young females mobilizing rapidly in the post-operative period. Pre-treatment with a small dose of non-depolarizing muscle relaxant (e.g. gallamine), diazepam or dantrolene have all been used with limited success in an attempt to reduce this unpleasant side-effect.

• Intra-occular pressure (IOP)is raised by about 10 mmHg for a matter of minutes following suxamethonium (normal range 1015 mmHg) and is significant in the presence of a globe perforation. However, concurrently administered thiopentone will offset this rise so that IOP remains static or may even fall. The mechanism by which suxamethonium increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils and transient dilation of choroidal blood vessels.

• Intragastric pressurerises by about 10 cmH2O, but as the lower oesophageal sphincter tone increases simultaneously there is no increased risk of reflux.

- Anaphylaxissuxamethonium makes up a significant proportion of the cases of anaphylaxis caused by muscle relaxants.
- Malignant hyperthermia (see below).
- Prolonged neuromuscular block (see below).
- Malignant hyperthermia (MH)

MH is a rare (1 in 200 000 in the UK), autosomal-dominant condition.

Mechanism

Trigger agents (essentially suxamethonium and the volatile anaesthetics) precipitate excessive Ca2+ release from the sarcoplasmic reticulum, which activates the contractile mechanisms within muscle, resulting in generalized muscle rigidity. ATP consumption is high causing increased CO2, heat and lactate production. Cells eventually break down resulting in myoglobinaemia and hyperkalaemia. The ryanodine receptor (on chromosome 19) has been closely associated with MH.

Treatment

This requires intravenous dantrolene (increments of 1 mg.kg1 up to 10 mg.kg1), aggressive cooling (using ice-cold saline to lavage bladder and peritoneumif open), and correction of abnormal biochemical and haematological parameters. Treatment should continue on ITU and should only stop when symptoms have completely resolved, otherwise it may recur. Before the introduction of dantrolene in 1979 the mortality rate was as high as 70%, but is now less than 5%.

Diagnosis

The diagnosis of MH is based on the response of biopsied muscle to 2% halothane and caffeine (2 mmol.l1). Patients are labelled either 'susceptible' (MHS)when positive to both halothane and caffeine, 'equivocal' (MHE)when positive to either halothane or caffeine, or 'non-susceptible' (MHN)when negative to halothane and caffeine.

Safe Drugs

These include opioids, thiopentone, propofol, etomidate, ketamine, benzodiazepines, droperidol, atropine, local anaesthetics and N2O.

Patients suspected of having MH should be referred to the UK MH investigation unit in Leeds.

Dantrolene is used in the treatment (and prophylaxis) of MH, neuroleptic malignant syndrome and chronic spasticity of voluntary muscle. It is available as capsules and in vials as an orange powder containing dantrolene 20 mg, mannitol 3 g and sodium hydroxide. Each vial should be reconstituted with 60 ml water

producing a solution of pH 9.5. It is highly irritant when extravasated and a diuresis follows intravenous administration reflecting its formulation with mannitol. Chronic use is associated with hepatitis and pleural effusion.

Mechanism of Action

Dantrolene uncouples the excitation contraction process by preventing the release of Ca2+ from the sarcoplasmic reticulum in striated muscle. As vascular smooth muscle and cardiac muscle are not primarily dependent on Ca2+ release for contraction, they are not usually affected. It has no effect on the muscle action potential and usually has little effect on the clinical duration of the non-depolarizing muscle relaxants. It may, however, produce respiratory failure secondary to skeletal muscle weakness.

Kinetics

Oral bioavailability is variable and it is approximately 85% bound in the plasma to albumin. It is metabolized in the liver and excreted in the urine.

- Prolonged block (suxamethonium apnoea)

Plasma cholinesterase activity may be reduced due to genetic variability or acquired conditions, leading to prolonged neuromuscular block. Single amino acid substitutions are responsible for genetically altered enzymatic activity. Four allelesusual (normal), atypical (dibucaine-resistant), silent (absent) and fluoride-resistanthave been identified at a single locus of chromosome 3, and make up the 10 genotypes.

Ninety six percent of the population is homozygous for the normal Eu gene and metabolize suxamethonium rapidly. Up to 4% may be heterozygotes resulting in a mildly prolonged block of up to 10 minutes while a very small fraction may have a genotype that confers a block of a few hours. This prolonged block may be reversed by administration of fresh frozen plasma, which provides a source of plasma cholinesterase. Alternatively the patient may be sedated and ventilated while the block wears off naturally.

Dibucaine (cinchocaine) is an amide local anaesthetic that inhibits normal plasma cholinesterase. However, it inhibits the variant forms of plasma cholinesterase less effectively. At a concentration of 105 mol.l1, using benzylcholine as a substrate, dibucaine inhibits the Eu:Eu form by 80% but the Ea:Ea form by only 20%. Other combinations are inhibited by 2080% depending on the type involved. The percentage inhibition is known as the 'Dibucaine number' and indicates the genetic makeup for an individual but makes no assessment of the quantity of enzyme in the plasma (Table 11.2).

Acquired factors associated with reduced plasma cholinesterase activity include:

- pregnancy

Table 11.2: Some genetic variants of plasma cholinesterase.

Genotype	Incidence	Duration of block	Dibucaine number
Eu:Eu	96%	normal	80
Eu:Ea	1:25	+	60
Eu:Es	1:90	+	80
Eu:Ef	1:200	+	75
Ea:Ea	1:2800	+ + + +	20
Ea:Ef	1:20 000	+ +	50
Es:Ea	1:29 000	+ + + +	20
Es:Es	1:100 000	+ + + +	
Ef:Es	1:150 000	+ +	60
Ef:Ef	1:154 000	+ +	70

- liver disease
- renal failure
- cardiac failure
- thyrotoxicosis
- cancer
- drugseither directly or by acting as substrate or inhibitor to AChE. Ecothiopate, metoclopramide, ketamine, the oral contraceptive pill, lithium, lignocaine, ester local anaesthetics, cytotoxic agents, edrophonium, neostigmine and trimetaphan

Decamethonium

$(CH_3)_3N^+-(CH_2)_{10}-N^+(CH_3)_3$

This bisquaternary depolarizing muscle relaxant has a slow onset (35 minutes) and a moderate duration of action (1020 minutes). It is excreted almost entirely unchanged in the urine. It has good cardiovascular stability, minimal histamine release and produces less myalgia than suxamethonium.

Non-Depolarizing Muscle Relaxants

Non-depolarizing muscle relaxants inhibit the actions of ACh at the NMJ by binding competitively to the a subunit of the nicotinic ACh receptor on the post-junctional membrane.

There is a wide safety margin at the NMJ to ensure muscle contraction, so that more than 70% of receptors need to be occupied by muscle relaxant before neuromuscular blockade can be detected by a peripheral nerve stimulator. The non-depolarizing block has essentially the same characteristics as the Phase II block (Table 11.1).

There are two chemical groupings:

- aminosteroidal compoundsvecuronium, pancuronium, rocuronium
- benzylisoquinolinium compoundstubocurarine, atracurium, mivacurium

Across the two chemical groups the drugs can be divided according to their duration of action:

- shortmivacurium
- intermediateatracurium
- longpancuronium

Owing to their relatively polar nature, non-depolarizing drugs are unable to cross lipid membranes resulting in a small volume of distribution. Some are hydrolysed in the plasma (atracurium, mivacurium) while others undergo a degree of hepatic metabolism (pancuronium, vecuronium). The unmetabolized fraction is excreted in the urine or bile.

Muscle relaxants are never given in isolation and so their potential for drug interaction should be considered (Table 11.3).

Tubocurarine (dTC)

Curare is a generic term used to describe various alkaloids from the plant species *Chondrodendron.* It was used in South America to poison the tips of hunting arrows.

dTC, which was first used as an aid to anaesthesia in 1942, is a monoquaternary alkaloid with a tertiary amine group, which is largely protonated at body pH.

Presentation and Uses

dTC is presented as a colourless solution containing 10 mg.ml1. At 0.5 mg.kg1 intubating conditions are reached within 3 minutes. Its duration of action is about 40 minutes, but this is variable.

Other Effects

- CardiovasculardTC causes the greatest degree of autonomic ganglion blockade and histamine release of all the non-depolarizing muscle relaxants, which results in a fall in blood pressure. Reflex tachycardia is uncommon due to the ganglion blockade. It appears to protect against arrhythmias.
- Gutit increases salivation.
- Toxicityanaphylaxis is associated with its use.

Table 11.3: Interaction of muscle relaxants with other drugs, and response to various physiological conditions.

Drug	Effect on blockade	Mechanism
Volatile anaesthetics	prolonged	depression of somatic reflexes in CNS (reducing transmitter release at the NMJ)
Aminoglycosides (large intraperitoneal doses), polymyxins and tetracycline	prolonged	decreased ACh release possibly by competition with Ca2+ (which unpredictably reverses the block)
Local anaesthetics	variable	low doses of local anaesthetic may enhance blockade by causing a degree of Na+ channel blockade
Lithium	prolonged	Na+ channel blockade
Diuretics	variable	variable effect on cAMP. May have effects via serum K+
Ca2+ channel antagonists	prolonged	reduced Ca2+ influx leading to reduced ACh release
Physiology		
Hypothermia	prolonged	reduced metabolism of muscle relaxant
Acidosis	variable	prolonged in most, but reduced for gallamine. The tertiary amine group of dTC becomes protonated increasing its affinity for the ACh receptor
Hypokalaemia	variable	acute hypokalaemia increases (i.e. makes more negative) the resting membrane potential. Non-depolarizing relaxants are potentiated while depolarizing relaxants are antagonized. The reverse is true in hyperkalaemia
Hypermagnesaemia	prolonged	decreased ACh release by competition with Ca2+, and stabilization of the post-junctional membrane. When used at supranormal levels (e.g. pre-eclampsia) Mg2+ can cause apnoea via a similar mechanism

Kinetics

dTC is 3050% protein-bound. Under acidic conditions the tertiary amine group (pKa 8.0) becomes increasingly protonated, resulting in increased potency. However, as pH varies, [K+] also varies, which alters the membrane potential and may offset altered potency. Elimination is independent of metabolism with 70% excreted in the urine and 30% in bile as unchanged drug. It accumulates in patients with renal failure in whom a greater proportion is excreted in the bile.

Pancuronium

Pancuronium is a bisquaternary aminosteroidal compound.

Presentation and Uses

Pancuronium is presented as a colourless solution containing 4 mg in 2 ml and should be stored at 4°C. At 0.1 mg.kg1 intubating conditions are reached within 90150 seconds. Its duration of action is about 45 minutes.

Other Effects

• Cardiovascularpancuronium causes a tachycardia by blocking cardiac muscarinic receptors. It may also have indirect sympathomimetic actions by preventing the uptake of noradrenaline at post-ganglionic nerve endings.

Kinetics

Between 10 and 40% is plasma protein-bound, and in keeping with other drugs in its class pancuronium has a low volume of distribution. About 35% is metabolized in the liver by de-acetylation to 3- and 17-hydroxy and 3,17-dihydroxy-pancuronium, the former of which is half as potent as pancuronium. Unchanged drug is eliminated mainly in the urine while its metabolites are excreted in bile.

Vecuronium

Vecuronium is a 'clean' drug, so called because it does not affect the cardiovascular system or precipitate the release of histamine. Its chemical structure differs from pancuronium by a single methyl group making it the monoquaternary analogue.

Presentation and Uses

Vecuronium is potentially unstable in solution and so is presented as 10 mg freezedried powder containing mannitol and sodium hydroxide and is dissolved in 5 ml water before administration. At 0.1 mg.kg1 satisfactory intubating conditions are reached in about 90120 seconds. It has a medium duration of action.

Other Effects

• Cardiovascularvecuronium has no cardiac effects but, unlike pancuronium or tubocurarine, it may leave unchecked the bradycardias associated with fentanyl and propofol.

• Myopathythere have been reports of myopathy following administration of the steroid-based relaxants when used by infusion for prolonged periods (> 6 days). This may persist for weeks or months.

Kinetics

Like pancuronium, vecuronium is metabolized in the liver by de-acetylation to 3-and 17-hydroxy and 3,17-dihydroxy-vecuronium. Again the 3-hydroxy metabolite carries significant muscle-relaxant properties but unlike 3-hydroxypancuronium it has a very short half-life and is of little clinical significance with normal renal function. With only a single charged quaternary ammonium group, it is more lipid soluble than pancuronium and despite the metabolism of a similar proportion in the liver, a far greater proportion is excreted in the bile. It may accumulate during administration by infusion.

Rocuronium

This aminosteroidal drug was developed from vecuronium and is structurally different at only four positions. Its main advantage is its rapid onset (intubating conditions within 6090 seconds) which in turn is due to its low potency.

A muscle relaxant with a low potency must be given at a higher dose to achieve a clinically significant effect. A higher number of molecules result in a greater concentration gradient from the plasma to the NMJ so that diffusion is faster and onset time is reduced.

Presentation and Uses

Rocuronium is prepared as a colourless solution containing 50 mg in 5 ml. At 0.6 mg.kg1 intubating conditions are reached within 100120 seconds, although this may be reduced to 60 seconds with higher doses (0.91.2 mg.kg1). Its duration of action is similar to that of vecuronium.

Other Effects

• Cardiovascularlike vecuronium it has minimal cardiovascular effects, although at high doses when used to facilitate a more rapid tracheal intubation, it may cause an increase in heart rate.

Table 11.4: Properties of some non-depolarizing muscle relaxants.

	Intubating dose (mg.kg1)	Speed of onset	Duration	Cardiovascular effects	Histamine release
Vecuronium	0.1	medium	medium	none/bradycardia	rare
Rocuronium	0.6	rapid	medium	none	rare
Pancuronium	0.1	medium	long	tachycardia	rare
Atracurium	0.5	medium	medium	none	slight
Cis-atracurium	0.2	medium	medium	none	rare
Doxacurium	0.05	very slow	long	none	rare
Mivacurium	0.2	medium	short	none	slight
Gallamine	2.0	fast	medium	tachycardia	rare
Tubocurarine	0.5	slow	long	hypotension	common

Kinetics

Rocuronium is mainly excreted unchanged in the bile and to a lesser extent in the urine, although some de-acetylated metabolites may be produced. Its duration of action may be prolonged in hepatic and renal failure.

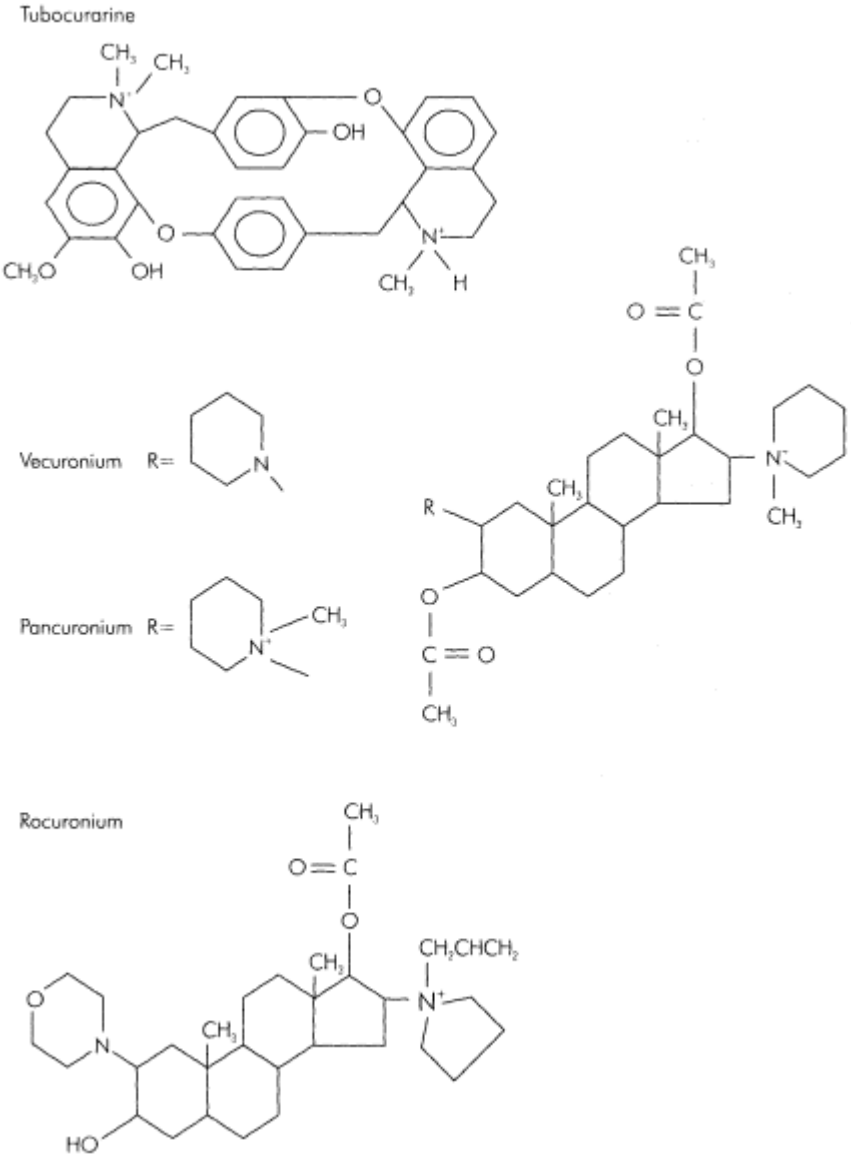


Figure 11.5:
Structure of some non-depolarizing muscle relaxants.

Atracurium

Atracurium is a benzylisoquinolinium compound that is formulated as a mixture of 10 stereoisomers, resulting from the presence of 4 chiral centres.

Presentation and Uses

Atracurium is presented as a colourless solution containing 10 mg.ml1 in 2.5, 5 and 25 ml vials and should be stored at 4°C. At 0.5 mg.kg1 intubating conditions are reached within 90120 seconds.

Other Effects

• CardiorespiratoryFollowing rapid administration it may precipitate the release of histamine, which may be localized to the site of injection but may be generalized resulting in bronchospasm and hypotension. Slow intravenous injection minimizes these effects.

Kinetics

Atracurium has a unique metabolic pathway, undergoing ester hydrolysis and Hofmann elimination.

• Ester hydrolysisnon-specific esterases unrelated to plasma cholinesterase are responsible for hydrolysis and account for 60% of atracurium's metabolism. The breakdown products are a quaternary alcohol, a quaternary acid and laudanosine. Unlike Hofmann elimination, acidic conditions accelerate this metabolic pathway. However, pH changes in the clinical range probably do not alter the rate of ester hydrolysis of atracurium.

• Hofmann eliminationwhile atracurium is stable at pH 4 and at 4°C, Hofmann elimination describes its spontaneous breakdown to laudanosine and a quaternary monoacrylate when placed at normal body temperature and pH. Acidosis and hypothermia will slow the process down. Both breakdown products have been shown to have potentially serious side-effects (i.e. seizures), but at concentrations in excess of those encountered clinically. Laudanosine, while being a glycine antagonist, has no neuromuscular-blocking properties and is cleared by the kidneys.

These metabolic pathways result in a drug whose elimination is independent of hepatic or renal function, which in certain clinical situations is advantageous.

Cis-Atracurium

Cis-atracurium is one of the 10 stereoisomers present in atracurium.

Presentation and Uses

Cis-atracurium is presented as a colourless solution containing 2 or 5 mg.ml1 and should be stored at 4°C. It is about three to four times more potent than atracurium and, therefore, has a slower onset time. However, the onset time can be improved by increasing the dose as its potential for histamine release is extremely low.

Kinetics

Cis-atracurium has a similar kinetic profile to atracurium. However, it does not undergo direct hydrolysis by plasma esterases and the predominant pathway for its elimination is Hofmann elimination to laudanosine and a monoquaternary acrylate. This is then hydrolysed by non-specific plasma esterases to a monoquaternary alcohol and acrylic acid. All of its metabolites are void of neuromuscular-blocking properties.

It has been used safely in children from 2 years of age and in elderly patients with minimal alteration of its kinetics. There is no change in its kinetic profile in patients with end-stage renal or hepatic impairment (Table 11.5).

Mivacurium

Mivacurium (a benzylisoquinolinium estersimilar to atracurium) is a chiral mixture of three stereospecific isomers in the following proportions:

- 36% cis-trans
- 58% trans-trans
- 6% cis-cis

Table 11.5: Kinetics some non-depolarizing muscle relaxants.

	Protein bound (%)	Volume of distribution (l.kg1)	Metabolized (%)	Elimination (%)	
				Bile	Urine
Pancuronium	2060	0.27	30	20	80
Vecuronium	10	0.23	20	70	30
Rocuronium	10	0.20	< 5	60	40
Atracurium	15	0.15	90	0	10
Cis-atracurium	15	0.15	95	0	5
Mivacurium	10	*0.210.32	90	0	5
Tubocurarine	3050	0.30	0	30	70
Gallamine	10	0.23	0	0	100

*lsomer specific

The cis-cis isomer has about 10% of the potency of the other two isomers and is not metabolized enzymatically. Its half-life is 10 times that of the other two isomers.

The main advantage of mivacurium is its short duration of action. Routine reversal of mivacurium with neostigmine may not be required due to its rapid enzymatic metabolism. In addition, neostigmine inhibits plasma cholinesterase and may prevent its metabolism. Edrophonium may be a more suitable agent for the reversal of neuromuscular block secondary to mivacurium.

Presentation and Uses

Mivacurium is presented as an acidic (pH 3.55.0) aqueous solution containing 2 mg.ml1 in 5 and 10 ml ampoules. It has a shelf life of 18 months when stored below 25°C.

Effects

- Cardiorespiratoryhigh doses may release histamine, resulting in a fall in blood pressure and bronchospasm.

Kinetics

Plasma cholinesterase is responsible for the metabolism of the cis-trans and transtrans isomers, so those patients with genetically low plasma cholinesterase levels (cf. suxamethonium apnoea) are subject to prolonged neuromuscular blockade. Its duration of action is significantly prolonged in patients with end-stage liver disease, mainly due to reduced plasma cholinesterase activity.

Doxacurium

This bisquaternary benzylisoquinolinium diester resembles atracurium. It is very potent but has a very slow onset of action. It has minimal effects on the cardiovascular system and releases little histamine. It is excreted unchanged in the urine and bile.

Gallamine

Gallamine was introduced into anaesthesia in 1947 as the first synthetic muscle relaxant. It currently has a limited role in anaesthesia, being used to reduce muscle fasciculations induced by suxamethonium.

It selectively blocks cardiac muscarinic receptors causing a tachycardia and may also activate the sympathetic nervous system. As it is excreted unchanged by the kidneys, renal failure significantly prolongs its half-life. Unlike other muscle relaxants an alkalosis prolongs its duration of action while an acidosis shortens it.

Anticholinesterases

The enzyme AChE hydrolyses ACh, terminating its effects. Anticholinesterases antagonize AChE so that more ACh is available at the NMJ. However, the actions of anticholinesterases are not specific to the NMJ and autonomic cholinergic effects (bradycardia, salivation) are also seen. For this reason they are often given with an anticholinergic (atropine or glycopyrrolate).

Three groups are defined based on their mechanism of action:

- easily reversible inhibition
- formation of a carbamylated enzyme complex
- irreversible inactivation by organophosphorous compounds

Easily Reversible Inhibition:
Edrophonium

Edrophonium is the only drug in this group. It is a phenolic quaternary amine.

Uses

At an intravenous dose of 210 mg it rapidly distinguishes between a myasthenic crisis (where muscle power is improved) and a cholinergic crisis (where the clinical picture is worsened).

Mechanism of Action

The quaternary amine group of edrophonium is attracted to the anionic site of AChE while its hydroxyl group forms a hydrogen bond at the esteratic site and stabilizes the complex (Figure 11.6). ACh is now unable to reach the active site of AChE. However, ACh competes with edrophonium for AChE because a true covalent bond is not formed between edrophonium and AChE. Edrophonium also causes increased ACh release.

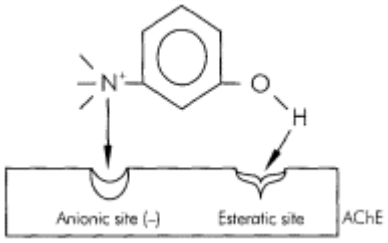


Figure 11.6:
Edrophonium forms an easily reversble enzyme complex.

Kinetics

Owing to its quaternary amine structure edrophonium has a low lipid solubility and is not absorbed following oral administration. For similar reasons it does not cross the bloodbrain barrier or the placenta. It has a faster onset of action than neostigmine. Up to 65% is excreted unchanged in the urine, the rest undergoes glucuronidation in the liver and subsequent excretion in the bile. It has only slight muscarinic side-effects but may still cause a bradycardia and salivation.

Formation of a Carbamylated Enzyme Complex

Neostigmine, pyridostigmine, physostigmine (Figure 11.7).

Mechanism of Action

Both ACh and the carbamate esters are hydrolysed when they react with AChE. However, ACh acetylates AChE while the carbamate esters produce a carbamylated enzyme (Figure 11.8). The later has a much slower rate of hydrolysis and so is unable to work for longerhence, it stops AChE hydrolysing ACh. The carbamate esters are also known as acid-transferring or time-dependent AChE inhibitors. Neostigmine also inhibits plasma cholinesterase and as such may prolong the actions of suxamethonium.

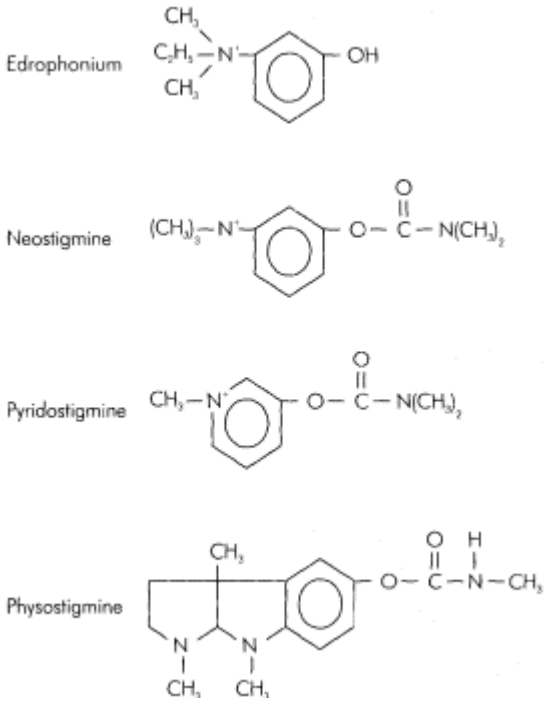


Figure 11.7:
Chemical structure of some anticholinesterases.

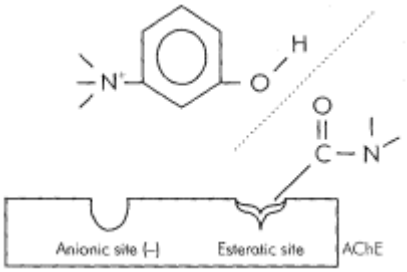


Figure 11.8:
Neostigmine forms a
carmabylated enzyme complex.

Neostigmine

Neostigmine is a quaternary amine.

Presentation and Uses

Neostigmine is available as tablets and in solution for intravenous injection (and in combination with glycopyrrolate). It is used to reverse the effects of nondepolarizing muscle relaxants (0.05 mg.kg1 intravenously), in the treatment of myasthenia gravis (1530 mg orally where effects last up to 4 hours) and in urinary retention.

Effects

• Cardiovascularif administered alone it will precipitate a bradycardia. It has a limited role in the treatment of supraventricular tachycardia.

• Respiratoryit may precipitate bronchospasm in asthmatics.

• Gutit increases salivation and intestinal motility, which may result in abdominal cramps.

Kinetics

Neostigmine is poorly absorbed from the gut and has a low oral bioavailability. It is minimally protein-bound, has a low volume of distribution and is partially metabolized in the liver. Approximately 55% is excreted unchanged in the urine.

Pyridostigmine is also a quaternary amine used mainly in the treatment of myasthenia gravis, where it is preferred to neostigmine because it has a longer duration of action and has fewer autonomic effects.

Kinetics

Pyridostigmine has a slower onset of action than neostigmine and its duration of action is longer. It relies on renal elimination more than neostigmine (75% excreted unchanged).

Like neostigmine it does not cross the bloodbrain barrier.

Physostigmine has a tertiary amine structure and it, therefore, has different properties. It is well absorbed from the gut and crosses the bloodbrain barrier. In the past it has been used in the treatment of anticholinergic poisoning.

Organophosphorous Compounds

Diisopropylfluorophosphonate (dyflos), tetraethylpyrophosphate (TEPP). These agents are highly lipid soluble and are, therefore, rapidly absorbed across skin.

Mechanism of Action

The esteratic site of AChE is phosphorylated by organophosphorous compounds resulting in inhibition of the enzyme (Figure 11.9). The complex that is formed is very stable and, unlike the carbamate esters, is resistant to hydrolysis or reactivation. In practice recovery depends on synthesis of new enzyme. These drugs also inhibit plasma cholinesterase.

Toxic manifestations include nicotinic and muscarinic effects, autonomic instability and initially central excitation progressing to depression, coma and apnoea.

Pralidoxime and obidoxine are reactivators of phosphorylated AChE by promoting hydrolysis. Atropine, anticonvulsants and ventilation may also be necessary in organophosphorous poisoning.

Ecothiopate is an organophosphorous compound that also has a quaternary ammonium group. It phosphorylates AChE resulting in a stable complex. It was used to treat narrow angle glaucoma and is associated with prolonged apnoea following suxamethonium.

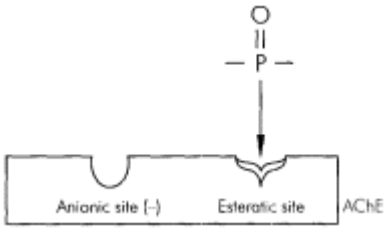


Figure 11.9:
Organophosphorus compounds phosphorylate AChE forming a very stable complex.

SECTION 3
CARDIOVASCULAR DRUGS

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12
Sympathomimetics

Physiology

Autonomic Nervous System (ANS)

The ANS is a complex system of neurones that controls the body's internal milieu. It is not under voluntary control and is anatomically distinct from the somatic nervous system. Its efferent limb controls individual organs and smooth muscle, while its afferent limb relays information (occasionally in somatic nerves) concerning visceral sensation and may result in reflex arcs.

The hypothalamus is the central point of integration of the ANS, but is itself under the control of the neocortex. However, not all autonomic activity involves the hypothalamus: locally, the gut coordinates its secretions; some reflex activity is processed within the spinal cord; the control of vital functions by baroreceptors is processed within the medulla. The ANS is divided into the parasympathetic and sympathetic nervous systems.

Parasympathetic Nervous System (PNS)

The PNS is made up of pre- and post-ganglionic fibres. The pre-ganglionic fibres arise form two locations (Figure 12.1):

- Cranial nerves (III, VII, IX, X)which supply the eye, salivary glands, heart, bronchi, upper gastrointestinal tract (to the splenic flexure) and ureters

- Sacral fibres (S2,3,4)which supply distal bowel, bladder and genitals

All these fibres synapse within ganglia that are close to, or within, the effector organ. The post-ganglionic neurone releases acetylcholine, which acts via nicotinic receptors.

The PNS may be modulated by anticholinergics (see Chapter 18) and anti-cholinesterases (see Chapter 11).

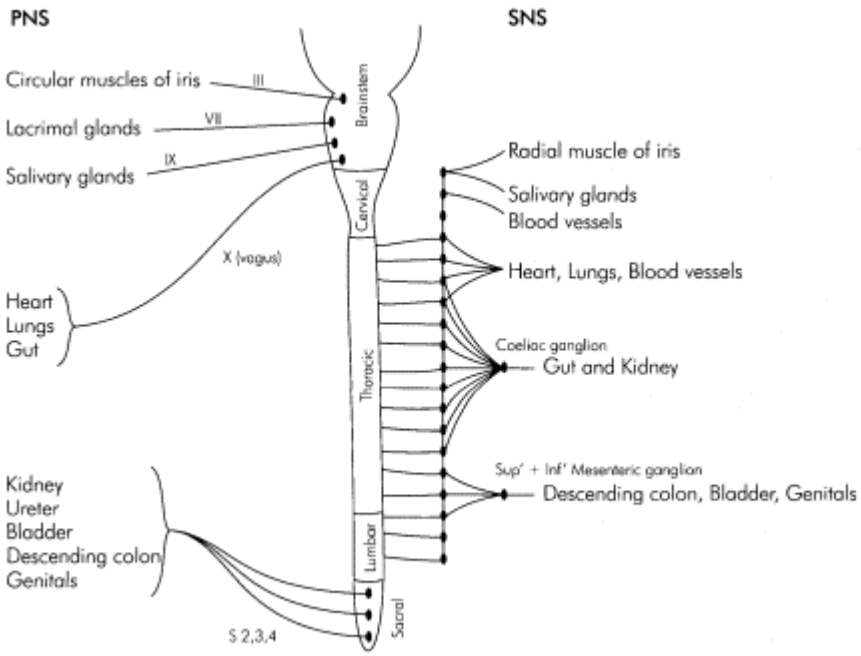

Figure 12.1:
Simplified diagram of the autonomic nervous system.

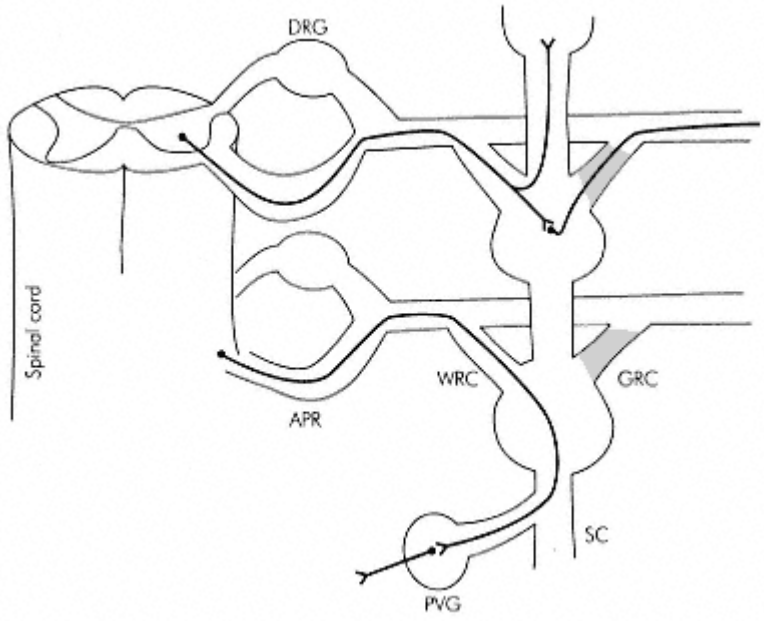

Figure 12.2:
Various connections of the sympathetic nervous system.
DRG, dorsal root ganglion; APR, anterior primary rami; WRC, white rami communicans; GRC, grey rami communicans; PVG, prevertebral ganglion. SC, sympathetic chain.

Sympathetic Nervous System (SNS)

The SNS is also made up of pre- and post-ganglionic fibres. The pre-ganglionic fibres arise within the lateral horns of the spinal cord at the thoracic and upper lumbar levels (T1L2) and pass into the anterior primary rami, and via the white rami communicans into the sympathetic chain or ganglia where they may either synapse at that or an adjacent level, or pass anteriorly through a splanchnic nerve to synapse in a prevertebral ganglion (Figure 12.2). The unmyelinated post-ganglionic fibres then pass into the adjacent spinal nerve via the grey rami communicans. They release noradrenaline, which acts via adrenoreceptors.

The adrenal medulla receives presynaptic fibres that synapse directly with its chromaffin cells using acetylcholine as the transmitter. It releases adrenaline into the circulation, which, therefore, acts as a hormone, not a transmitter.

Post-ganglionic sympathetic fibres that release acetylcholine innervate sweat glands.

All pre-ganglionic ANS fibres are myelinated and release acetylcholine, which acts via nicotinic receptors (Table 12.1).

Sympathomimetics

Sympathomimetics exert their effects via adrenoreceptors or dopamine receptors either directly or indirectly. Direct-acting sympathomimetics attach to and act directly via these receptors, while indirect-acting sympathomimetics cause the release of noradrenaline to produce their effects via these receptors.

The structure of sympathomimetics is based on a benzene ring with various amine side-chains attached at the C1 position. Where a hydroxyl group is present at the C3 and C4 positions the agent is known as a catecholamine (because 3,4-dihydroxybenzene is otherwise known as 'catechol').

Sympathomimetic and other inotropic agents will be discussed under the following headings:

- Naturally occurring catecholamines
- Synthetic agents
- Other inotropic agents

Table 12.1: Summary of transmitters within the autonomic nervous system.

	Pre-ganglionic	Post-ganglionic
PNS	acetylcholine	acetylcholine
SNS	acetylcholine	noradrenaline
Adrenal medulla	acetylcholine	
Sweat glands	acetylcholine	acetylcholine

Naturally Occurring Catecholamines

Adrenaline, noradrenaline and dopamine are the naturally occurring catecholamines and their synthesis is interrelated (Figure 12.3). They act via adrenergic and dopaminergic receptors, which are summarized in Table 12.2.

Adrenaline

Presentation and Uses

Adrenaline is presented as a clear solution containing 0.11 mg.ml1 for administration as a bolus in asystole or anaphylaxis or by infusion (dose range 0.010.5 µg.kg1.min1) in the critically ill with circulatory failure. It may also be nebulized into the upper airway where its vasoconstrictor properties will temporarily reduce the swelling associated with acute upper airway obstruction. A 1% ophthalmic solution is used in open-angle glaucoma, and a metered dose inhaler delivering 280 µg for treatment of anaphylaxis associated with insect stings or drugs. In addition, it is presented in combination with local anaesthetic solutions at a strength of 1 in 80 000200 000.

Mechanism of Action

Adrenaline exerts its effects via a and b adrenoreceptors. a1 Adrenoreceptor activation stimulates phospholipase C (via Gq) (cf. p31), which hydrolyses phosphatidylinositol bisphosphate (PIP2). Inositol triphosphate (IP3) is released which leads to increased Ca2+ availability within the cell. a2 Adrenoreceptor activation is coupled to Gi proteins that inhibit adenylate cyclase and reduce cAMP concentration. b Adrenoreceptors are coupled to Gs proteins that activate adenylate cyclase, leading to an increase in cAMP and specific phosphorylation depending on the site of the adrenoreceptor.

Effects

• Cardiovasculathe effects of adrenaline vary according to dose. When administered as a low-dose infusion, b effects predominate. This produces an increase in cardiac output, myocardial oxygen consumption, coronary artery dilatation and reduces the threshold for arrhythmias. Peripheral b effects may result in a fall in diastolic blood pressure and peripheral vascular resistance. At high doses by infusion or when given as a 1 mg bolus during cardiac arrest, a1 effects predominate causing a rise in systemic vascular resistance. It is often used in combination with local anaesthetics to produce vasoconstriction before dissection during surgery. When used with halothane, the dose should be restricted to 100 µg per 10 minutes to avoid arrhythmias. It should not be infiltrated into areas supplied by end arteries lest their vascular supply become compromised. Extravasation can cause tissue necrosis.

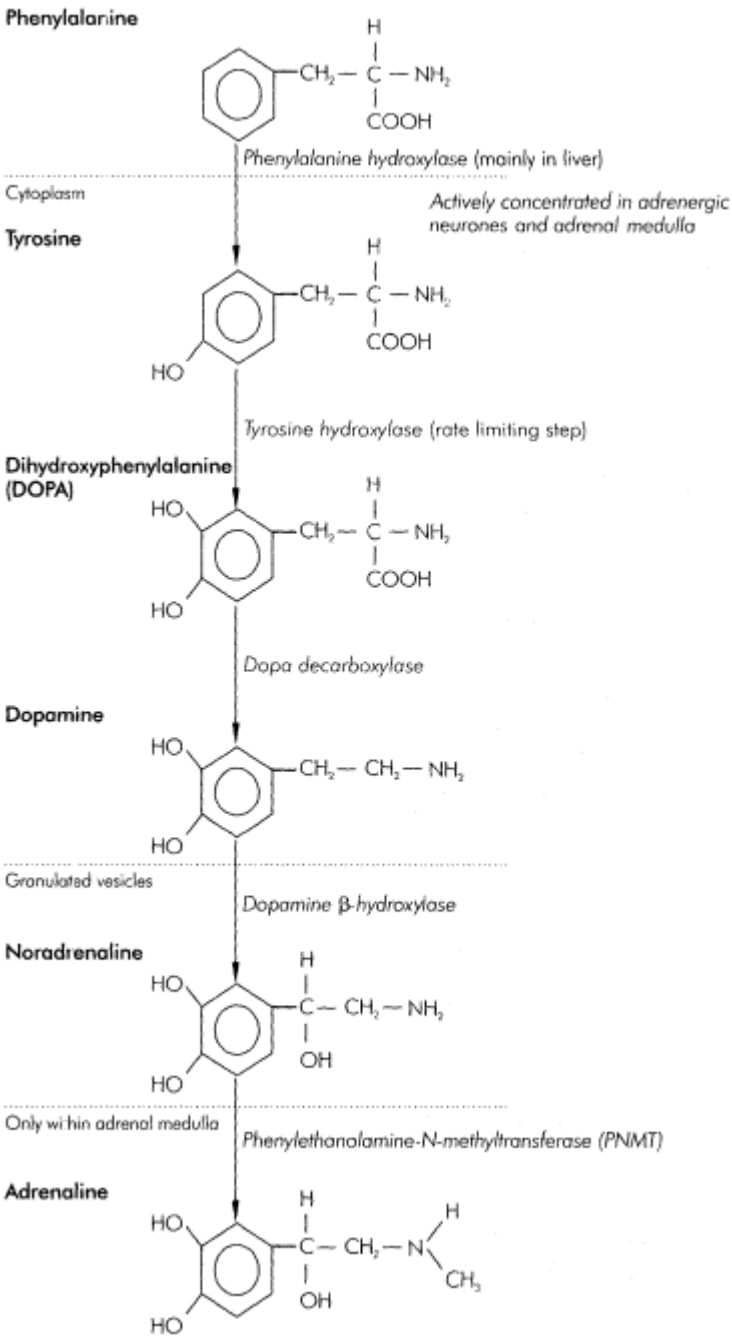

Figure 12.3:
Catecholamine synthesis.

• Respiratoryadrenaline produces a small increase in minute volume. It has potent bronchodilator effects although secretions may become more tenacious. Pulmonary vascular resistance is increased.

• Metabolicadrenaline increases the basal metabolic rate. It raises plasma glucose by stimulating glycogenolysis (in liver and skeletal muscle), lipolysis and gluconeogenesis. Initially insulin secretion is increased (a b2 effect) but is often overridden by an a effect which inhibits its release and compounds the increased glucose production. Glucagon secretion and plasma lactate are also raised. Lipase activity is augmented resulting in increased free fatty acids which leads to increased fatty acid oxidation in the liver and ketogenesis. These metabolic effects limit its use, especially in those with diabetes. Na+ reabsorption is increased by direct stimulation of tubular Na+ transport and by stimulating renin and, therefore, aldosterone production. b2 Receptors are responsible for the increased transport of K+ into cells, which follows an initial temporary rise as K+ is released from the liver.

• Central nervous systemit increases MAC, and increases the peripheral pain threshold.

• Renalrenal blood flow is moderately decreased and the increase in bladder sphincter tone may result in difficulty in micturition.

Kinetics

Adrenaline is not given orally due to inactivation. Subcutaneous absorption is less rapid than intramuscular. Tracheal absorption is erratic but may be used in emergencies where intravenous access is not available.

It is metabolized by mitochondrial monoamine oxidase (MAO) and catechol O-methyl transferase (COMT) within the liver, kidney and blood to the inactive 3-methoxy4-hydroxymandelic acid (vanillylmandelic acid or VMA) and metadrenaline which is conjugated with glucuronic acid or sulphates, both of which are excreted in the urine. It has a short half-life (about 2 minutes) due to rapid metabolism.

Noradrenaline

Presentation and Uses

Noradrenaline is presented as a clear solution containing 0.22 mg.ml1 noradrenaline acid tartrate, which is equivalent to 0.11 mg.ml1 respectively of noradrenaline base, and contains the preservative sodium metabisulphite. It is used as an intravenous infusion (dose range 0.050.5 µg.kg1.min1) to increase the systemic vascular resistance.

Mechanism of Action

Its actions are mediated mainly via stimulation of a1 adrenoreceptors but also b adrenoreceptors.

Effects

• Cardiovascularthe effects of systemically infused noradrenaline are slightly different from those of endogenous noradrenaline. Systemically infused noradrenaline causes peripheral vasoconstriction, increases systolic and diastolic blood pressure and may cause a reflex bradycardia. Cardiac output may fall and myocardial oxygen consumption is increased. A vasodilated coronary circulation carries an increased coronary blood flow. Pulmonary vascular resistance may be increased and venous return is increased by venoconstriction. In excess it produces hypertension, bradycardia, headache and excessive peripheral vasoconstriction, occasionally leading to ischaemia and gangrene of extremities. Extravasation can cause tissue necrosis. Endogenously released noradrenaline causes tachycardia and a rise in cardiac output.

• Splanchnicrenal and hepatic blood flow falls due to vasoconstriction.

• Uterusblood flow to the pregnant uterus is reduced and may result in foetal bradycardia. It may also exert a contractile effect and cause foetal asphyxia.

• Interactionsdespite being a direct-acting sympathomimetic amine it should be used with caution in patients taking monoamine oxidase inhibitors (MAOI) as its effects may be exaggerated and prolonged.

Kinetics

For endogenously released noradrenaline, Uptake 1 describes its active uptake back into the nerve terminal where it is metabolized by MAO (COMT is not present in sympathetic nerves) or recycled. It forms the main mechanism by which noradrenaline is inactivated. Uptake 2 describes the diffusion away from the nerve and is less important. Noradrenaline reaches the circulation in this way and is metabolized by COMT and MAO to the inactive 3-methoxy4-hydroxymandelic acid (vanillylmandelic acid or VMA) and normetadrenaline which is conjugated with glucuronic acid or sulphates, both of which are excreted in the urine. It has a short half-life (about 2 minutes) due to rapid metabolism. Unlike adrenaline and dopamine, up to 25% is taken up as it passes through the lungs.

Dopamine

In certain cells within the brain and interneurones of the autonomic ganglia dopamine is not converted to noradrenaline, and is released as a neurotransmitter.

Table 12.2: Actions and mechanisms of adrenoreceptors.

Receptor	Subtype	Location	Actions when stimulated	Mechanism
a	1	vascular smooth muscle	vasoconstriction	Gq-coupled phospholipase C activated ® IP3® Ca2+
	2	widespread throughout the nervous system	sedation, analgesia, attenuation of sympathetically mediated responses	Gi-coupled adenylate cyclase inhibited ® ¯ cAMP
		platelets	platelet aggregation	
b	1	heart	+ve inotropic and chronotropic effect	Gs-coupled adenylate cyclase activated ® cAMP
	2	bronchi, vascular smooth muscle, uterus (and heart)	relaxation of smooth muscle	Gs-coupled adenylate cyclase activated ® cAMP ® Na+/K+ ATPase activity and hyperpolarization
	3	adipose tissue	lipolysis	Gs-coupled adenylate cyclase activated ® cAMP
D	1	within the central nervous system	modulates extra-pyramidal activity	Gs-coupled adenylate cyclase activated ® cAMP
		peripherally	vasodilatation of renal and mesenteric vasculature	
	2	within the central nervous system	reduced pituitary hormone output	Gi-coupled adenylate cyclase inhibited ® ¯ cAMP
		peripherally	inhibit further noradrenaline release	

Presentation and Uses

Dopamine is presented as a clear solution containing 200 or 800 mg in 5 ml water with sodium metabisulphite. It is used to improve haemodynamic parameters and urine output.

Mechanism of Action

In addition to its effects on a and b adrenoreceptors, dopamine also acts via dopamine (D1 and D2) receptors via Gs and Gi coupled adenylate cyclase leading to increased or decreased levels of cAMP.

Effects

• Cardiovasculartheseдepend on its rate of infusion and vary between patients. At lower rates (up to 10 µg.kg1.min1) b1 effects predominate leading to increased contractility, heart rate, cardiac output and coronary blood flow. In addition to its direct effects, it also stimulates the release of endogenous noradrenaline. At higher rates (> 10 µg.kg1.min1) a effects tend to predominate leading to increased systemic vascular resistance and venous return. In keeping with other inotropes an adequate preload is essential to help control tachycardia. It is less arrhythmogenic than adrenaline. Extravasation can cause tissue necrosis.

• Respiratoryinfusions of dopamine attenuate the response of the carotid body to hypoxaemia. Pulmonary vascular resistance is increased.

• Splanchnicdopamine has been shown to vasodilate mesenteric vessels via D1 receptors. However, the improvement in urine output may be entirely due to inhibition of proximal tubule Na+ reabsorption and an improved cardiac output and blood pressure.

• Central nervous systemdopamine modulates extra-pyramidal movement and inhibits the secretion of prolactin from the pituitary gland. It cannot cross the bloodbrain barrier, although its precursor L-dopa can.

• MiscellaneousOwing to stimulation of the chemoreceptor trigger zone it causes nausea and vomiting. Gastric transit time is also increased.

• Interactionsdespite being a direct-acting sympathomimetic amine the effects of dopamine may be significantly exaggerated and prolonged during MAOI therapy.

Kinetics

Dopamine is only administered intravenously and preferably via a central vein. It acts within 5 minutes and has a duration of 10 minutes. Metabolism is via MAO and COMT in the liver, kidneys and plasma to inactive compounds (3,4-dihydroxyphenylacetic acid and homovanillic acid (HVA)) which are excreted in the urine as sulphate and glucuronide conjugates. About 25% of an administered dose is converted to noradrenaline in sympathetic nerve terminals. Its half-life is about 3 minutes.

Synthetic Agents

Of the synthetic agents, only isoprenaline, dobutamine and dopexamine are classified as catecholamines as only they contain hydroxyl groups on the 3- and 4-positions of the benzene ring.

a*1 Agonists:*
Phenylephrine

Phenylephrine is a direct-acting sympathomimetic amine with potent a1 agonist actions. It causes a rapid rise in systemic vascular resistance and blood pressure. It has no effect on b adrenoreceptors.

Presentation and Uses

Phenylephrine is presented as 10 mg white powder, which should be dissolved and then diluted before use. Bolus doses of 50100 µg are used intravenously although 25 mg may be administered intramuscularly or subcutaneously for a more prolonged duration. It is used to increase a low systemic vascular resistance associated with spinal anaesthesia or systemically administered drugs. In certain patients, general anaesthesia may drop the systemic vascular resistance and reverse a left to right intracardiac shunt, this may be reversed by phenylephrine. It is also available for use as a nasal decongestant, mydriatic and in combination with a corticosteroid/local anaesthetic paste in the symptomatic relief of external piles. It may have a limited use in the treatment of supraventricular tachycardia associated with hypotension.

Effects

- Cardiovascularphenylephrine raises the systemic vascular resistance and blood pressure and may result in a reflex bradycardia, which probably causes the drop in cardiac output that may accompany its use. It is not arrhythmogenic.
- Central nervous systemit has no stimulatory effects.
- Renalblood flow falls in a manner similar to that demonstrated by noradrenaline.
- Uterusit reduces the uteroplacental blood flow and its use is avoided in pregnancy.

Kinetics

Intravenous administration results in a rapid rise in blood pressure which lasts 510 minutes, while intramuscular or subcutaneous injection takes 15 minutes to work but lasts up to 1 hour. It is metabolized in the liver by MAO. The products of metabolism and their route of elimination have not been identified.

Methoxamine

Methoxamine is a direct-acting sympathomimetic amine with specific a1 agonist actions. Consequently it has similar effects to phenylephrine. It is presented as a clear solution containing 20 mg.ml1.

An intravenous bolus of 1 mg usually produces a rapid rise in systemic vascular resistance and, therefore, blood pressure, often with an accompanying reflex bradycardia. It may also be given intramuscularly or subcutaneously at a higher dose for a more prolonged duration of action.

Like phenylephrine it reduces the uteroplacental blood flow and its use is avoided in pregnancy.

b *Agonists:*
Isoprenaline

Isoprenaline is a highly potent synthetic catecholamine with actions at b1 and b2 adrenoreceptors. It has no a effects.

Presentation and Uses

Isoprenaline is presented as a clear solution containing 1 mg.ml1 for intravenous infusion and as a metered dose inhaler delivering 80 or 400 µg. It is no longer used to treat reversible airway obstruction as this was associated with an increased mortality. More specific b2 agonists are now used (e.g. salbutamol). The 30 mg tablets are only very rarely used. It is used intravenously to treat severe bradycardia associated with AV block or b-blockers (dose range 0.510 µg.min1).

Effects

- Cardiovascularstimulation of b1 adrenoreceptors increases heart rate, myocardial contractility, automaticity and cardiac output. The effects on blood pressure are varied. The b2 effects may drop the systemic vascular resistance so that the increase in cardiac output is insufficient to maintain blood pressure. Myocardial oxygen delivery may decrease significantly when tachycardia reduces diastolic coronary filling time and the reduced diastolic blood pressure reduces coronary perfusion. Some coronary vasodilatation occurs to attenuate this.

- Respiratoryit is a potent bronchodilator and inhibits histamine release in the lungs, improving mucous flow. Anatomical dead space and ventilation perfusion mismatching increases which may lead to systemic hypoxaemia.

- Central nervous systemisoprenaline has stimulant effects on the CNS.

- Splanchnicmesenteric and renal blood flow is increased.

- Metabolicits b effects lead to a raised blood glucose and free fatty acids.

Kinetics

When administered orally it is well absorbed but extensive first-pass metabolism results in a low oral bioavailability, being rapidly metabolized by COMT within the liver. A significant fraction is excreted unchanged in the urine along with conjugated metabolites.

Dobutamine

Dobutamine is a direct-acting synthetic catecholamine derivative of isoprenaline. b1 Effects predominate but it retains a small effect at b2 adrenoreceptors.

Presentation and Uses

Dobutamine is presented in 20 ml water containing 250 mg dobutamine and sodium metabisulphite or in 5 ml water containing 250 mg dobutamine and ascorbic acid. It is used to augment low cardiac output states associated with myocardial infarction, cardiac surgery, and cardiogenic shock (dose range 0.520 µg.kg1.min1). It is also used in cardiac stress testing as an alternative to exercise.

Effects

• Cardiovascularits main actions are direct stimulation of b1 receptors resulting in increased contractility, heart rate and myocardial oxygen requirement. The blood pressure is usually increased despite a limited fall in systemic vascular resistance via b2 stimulation. It may precipitate arrhythmias including an increased ventricular response rate in patients with atrial fibrillation or flutter, due to increased AV conduction. It should be avoided in patients with cardiac outflow obstruction (e.g. aortic stenosis, cardiac tamponade).

• Splanchnicit has no effect on the splanchnic circulation although urine output may increase following a rise in cardiac output.

Kinetics

Dobutamine is only administered intravenously. It is rapidly metabolized by COMT to inactive metabolites that are conjugated and excreted in the urine. It has a half-life of 2 minutes.

Dopexamine

Dopexamine is a synthetic analogue of dopamine.

Presentation and Uses

Dopexamine is presented as 50 mg in 5 ml (at pH 2.5) of clear solution for intravenous use. It is used to improve cardiac output and improve mesenteric perfusion (dose range 0.56 µg.kg1.min1).

Mechanism of Action

Dopexamine stimulates b2 adrenoreceptors and dopamine (D1) receptors and may also inhibit the re-uptake of noradrenaline. It has only minimal effect on D2 and b1 adrenoreceptors, and no effect on a adrenoreceptors.

Effects

• Cardiovascularwhile it has positive inotropic effects (due to cardiac b2 receptors), improvements in cardiac output are aided by a reduced afterload due to peripheral b2 stimulation, which may reduce the blood pressure. It produces a small increase in coronary blood flow and there is no change in myocardial oxygen extraction. The alterations in heart rate are varied and it only rarely precipitates arrhythmias.

• Mesenteric and renalblood flow to the gut and kidneys increases due to an increased cardiac output and reduced regional vascular resistance. Urine output increases. It may cause nausea and vomiting.

• Respiratorybronchodilation is mediated via b2 stimulation.

• Miscellaneoustremor and headache have been reported.

Kinetics

Dopexamine is cleared rapidly from the blood and has a half-life of 7 minutes.

Salbutamol

Salbutamol is a synthetic sympathomimetic amine with actions mainly at b2 adrenoreceptors.

Presentation and Uses

Salbutamol is presented as a clear solution containing 50500 µg.ml1 for intravenous infusion after dilution, a metered dose inhaler (100 µg) and a dry powder (200400 µg) for inhalation, a solution containing 2.55 mg.ml1 for nebulization, and oral preparations (syrup 0.4 mg.ml1 and 2, 4 or 8 mg tablets). It is used in the treatment of reversible lower airway obstruction and occasionally in premature labour.

Effects

• Respiratoryits main effects are relaxation of bronchial smooth muscle. It reverses hypoxic pulmonary vasoconstriction, increasing shunt and,

may lead to hypoxaemia. Adequate oxygen should, therefore, be administered with nebulized salbutamol.

• Cardiovascularthe administration of high doses, particularly intravenously, can cause stimulation of b1 adrenoreceptors resulting in tachycardia, which may limit the dose. Lower doses are sometimes associated with b2-mediated vasodilatation, which may reduce the blood pressure. It may also precipitate arrhythmias, especially in the presence of hypokalaemia.

• MetabolicNa+/K+ ATPase is stimulated and transports K+ into cells resulting in hypokalaemia. Blood sugar rises especially in diabetic patients and is exacerbated by concurrently administered steroids.

• Uterusit relaxes the gravid uterus. A small amount crosses the placenta to reach the foetus.

• Miscellaneousa direct effect on skeletal muscle may produce tremor.

Kinetics

The absorption of salbutamol from the gut is incomplete and is subject to a significant hepatic first-pass metabolism. Following inhalation or intravenous administration it has a rapid onset of action. It is 10% protein-bound and has a half-life of 46 hours. It is metabolized in the liver to the inactive 4-O-sulphate, which is excreted along with salbutamol in the urine.

Salmeterol

Salmeterol is a long-acting b2 agonist used in the treatment of nocturnal and exercise-induced asthma. It should not be used during acute attacks due to a relatively slow onset.

It has a long non-polar side-chain which binds to the b2 adrenoreceptor giving it a long duration of action (about 12 hours). It is 15 times more potent than salbutamol at the b2 adrenoreceptor, but four times less potent at the b1 adrenoreceptor. It prevents the release of histamine, leukotrienes and prostaglandin D2 from mast cells, and also has additional anti-inflammatory effects that differ from those induced by steroids.

Its effects are similar to those of salbutamol.

Ritodrine

Ritodrine is a b2 agonist that is used to treat premature labour. Tachycardia (b1 effect) is often seen during treatment. It crosses the placenta and may result in foetal tachycardia.

Ritodrine has been associated with fatal maternal pulmonary oedema. It also causes hypokalaemia, hyperglycaemia and, at higher levels, vomiting, restlessness and seizures.

Terbutaline

Terbutaline is a b2 agonist with some activity at b1 adrenoreceptors. It is used in the treatment of asthma and uncomplicated preterm labour. It has a similar side-effect profile to other drugs in its class.

*Mixed (*a *and* b*):*
Ephedrine

Ephedrine is found naturally in certain plants but is synthesized for medical use.

Presentation and Uses

Ephedrine is formulated as tablets, an elixir, nasal drops and as a solution for injection containing 30 mg.ml1. It can exist as four isomers but only the L-isomer is active. It is used intravenously to treat hypotension associated with regional anaesthesia particularly in obstetric practice. Here it is preferred to purer a1 agonists because it increases cardiac output and blood pressure without inducing a1-mediated vasoconstriction to uterine blood vessels, which would compromise foetal oxygenation. It is also used to treat bronchospasm, nocturnal enuresis and narcolepsy.

Mechanism of Action

Ephedrine has both direct and indirect sympathomimetic actions. It also inhibits the actions of MAO on noradrenaline.

Owing to its indirect actions it is prone to tachyphylaxis as noradrenaline stores in sympathetic nerves become depleted.

Effects

- Cardiovascularit increases the cardiac output, heart rate, blood pressure, coronary blood flow and myocardial oxygen consumption. Its use may precipitate arrhythmias.
- Respiratoryit is a respiratory stimulant and causes bronchodilation.
- Renalrenal blood flow is decreased and the glomerular filtration rate falls.
- Interactionsit should be used with extreme caution in those patients taking MAOI.

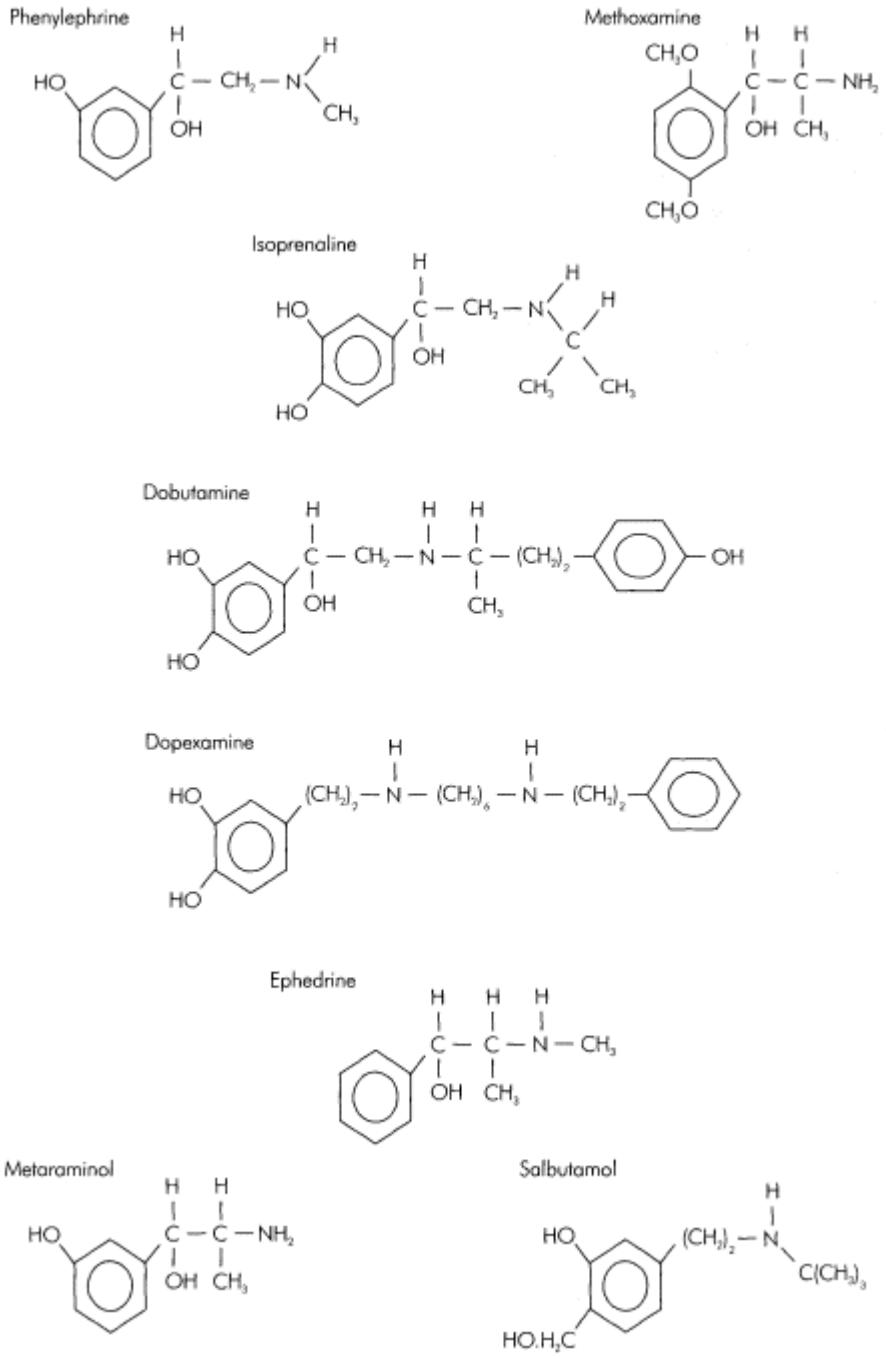

Figure 12.4:
Structure of some synthetic sympathomimetic amines.

Kinetics

Ephedrine is well absorbed orally, intramuscularly and subcutaneously. Unlike adrenaline it is not metabolized by MAO or COMT and, therefore, has a longer duration of action and an elimination half-life of 4 hours. Some is metabolized in the liver but 65% is excreted unchanged in the urine.

Metaraminol

Metaraminol is a synthetic amine with both direct and indirect sympathomimetic actions. It acts mainly via a1 adrenoreceptors but also retains some b adrenoreceptor activity.

Presentation and Uses

Metaraminol is presented as a clear solution containing 10 mg.ml1. It is used to correct hypotension associated with spinal or epidural anaesthesia. An intravenous bolus of 15 mg is usually sufficient.

Effects

• Cardiovascularits main actions are to increase systemic vascular resistance, which leads to an increased blood pressure. Despite its activity at b adrenoreceptors the cardiac output often drops in the face of the raised systemic vascular resistance. Coronary artery flow increases by an indirect mechanism. Pulmonary vascular resistance is also increased leading to raised pulmonary artery pressure. Like methoxamine, it reduces uterine artery blood flow, so it is not used to correct hypotension associated with regional anaesthesia in obstetric practice.

Other Inotropic Agents

Non-selective Phosphodiesterase Inhibitors:
Aminophylline

Aminophylline is a methylxanthine derivative. It is a complex of 80% theophylline and 20% ethylenediamine (which has no therapeutic effect but does improve solubility).

Presentation and Uses

Aminophylline is available as tablets and as a solution for injection containing 25 mg.ml1. Oral preparations are often formulated as slow release due to its half-life of about 6 hours. It is used in the treatment of asthma where the dose ranges from 450 to 1250 mg daily. When given intravenously during acute severe asthma a loading dose of 6 mg.kg1 over 20 minutes is given, followed by an infusion of 0.5

mg.kg1.h1. It may also be used to reduce the frequency of episodes of central apnoea in premature neonates. It is very occasionally used in the treatment of heart failure.

Mechanism of Action

Aminophylline is a non-selective inhibitor of all five phosphodiesterase isoenzymes, which hydrolyse cAMP and possibly cGMP, thereby increasing their intracellular levels. It may also directly release noradrenaline from sympathetic neurones and demonstrate synergy with catecholamines, which act via adrenoreceptors to increase intracellular cAMP. In addition it interferes with the translocation of Ca2+ into smooth muscle, inhibits the degranulation of mast cells by blocking their adenosine receptors and potentiates prostaglandin synthetase activity.

Effects

• Respiratoryaminophylline causes bronchodilation, improves the contractility of the diaphragm and increases the sensitivity of the respiratory centre to carbon dioxide. It works well in combination with b2 agonists due to the different pathway used to increase cAMP.

• Cardiovascularit has mild positive inotropic and chronotropic effects and causes some coronary and peripheral vasodilatation. It lowers the threshold for arrhythmias (particularly ventricular) especially in the presence of halothane.

• Central nervous systemthe alkyl group at the 1-position (also present in caffeine) is responsible for its central nervous system stimulation, resulting in a reduced seizure threshold.

• Renalthe alkyl group at the 1-position is also responsible for its weak diuretic effects. Inhibition of tubular Na+ reabsorption leads to a naturesis and may precipitate hypokalaemia.

• Interactionsco-administration of drugs that inhibit hepatic cytochrome P450 (cimetidine, erythromycin, ciprofloxacin and oral contraceptives) tend to delay the elimination of aminophylline and a reduction in dose is recommended. The use of certain selective serotonin re-uptake inhibitors (fluvoxamine) should be avoided with aminophylline as levels of the latter may rise sharply. Drugs that induce hepatic cytochrome P450 (phenytoin, carbamazepine, barbiturates and rifampicin) increase aminophylline clearance and the dose may need to be increased.

Kinetics

Aminophylline is well absorbed from the gut with a high oral bioavailability (> 90%). About 50% is plasma protein-bound. It is metabolized in the liver by cytochrome P450 to inactive metabolites and interacts with the metabolism of other drugs undergoing metabolism by a similar route. Owing to its low hepatic extraction ratio its metabolism is independent of liver blood flow. Approximately 10% is excreted unchanged in the urine. The effective therapeutic plasma concentration is 1020 µg.ml1. Cigarette smoking increases the clearance of aminophylline.

Toxicity

Above 35 µg.ml1, hepatic enzymes become saturated and its kinetics change from first- to zero-order resulting in toxicity. Cardiac toxicity manifests itself as tachyarrhythmias including ventricular fibrillation. Central nervous system toxicity includes tremor, insomnia and seizures (especially following rapid intravenous administration). Nausea and vomiting are also a feature, as is rhabdomyolysis.

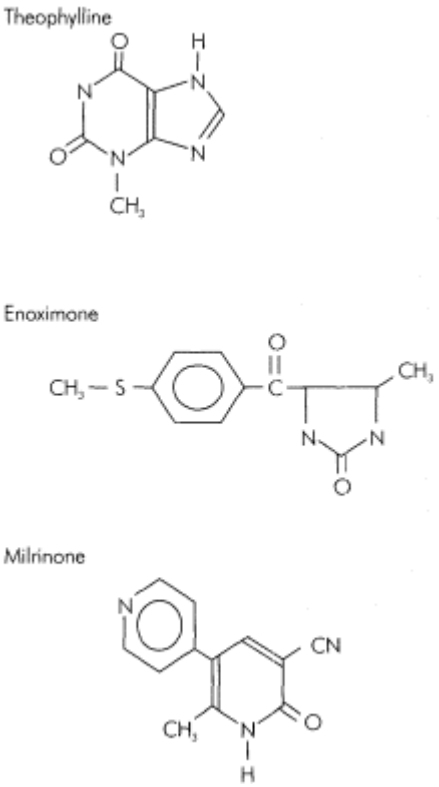

Figure 12.5:
Structure of some phosphodiesterase inhibitors.

Selective Phosphodiesterase Inhibitors:
Enoximone

The imidazolone derivative enoximone is a selective phosphodiesterase III inhibitor.

Presentation and Uses

Enoximone is available as a yellow liquid (pH 12) for intravenous use containing 5 mg.ml1. It is supplied in propyl glycol and ethanol and should be stored between 5 and 8°C. It is used to treat congestive heart failure and low cardiac output states associated with cardiac surgery. It should be diluted with an equal volume of water or 0.9% saline in plastic syringes (crystal formation is seen when mixed in glass syringes) and administered as an infusion of 520 µg.kg1.min1, which may be preceded by a loading dose of 0.5 mg.kg1, and can be repeated up to a maximum of 3 mg.kg1. Unlike the catecholamines it may take up to 30 minutes to act.

Mechanism of Action

Enoximone works by preventing the degradation of cAMP and possibly cGMP in cardiac and vascular smooth muscle. By effectively increasing cAMP within the myocardium, it increases the slow Ca2+ inward current during the cardiac action potential. This produces an increase in Ca2+ release from intracellular stores, and an increase in the Ca2+ concentration in the vicinity of the contractile proteins, and hence to a positive inotropic effect. By interfering with Ca2+ flux into vascular smooth muscle it causes vasodilatation.

Effects

• Cardiovascularenoximone has been termed an 'inodilator' due to its positive inotropic and vasodilator effects on the heart and vascular system. In patients with heart failure the cardiac output increases by about 30% while end diastolic filling pressures decrease by about 35%. The myocardial oxygen extraction ratio remains unchanged by virtue of a reduced ventricular wall tension and improved coronary artery perfusion. The blood pressure may remain unchanged or fall, the heart rate remains unchanged or rises slightly and arrhythmias occur only rarely. It shortens atrial, AV node and ventricular refractoriness. When used in patients with ischaemic heart disease a reduction in coronary perfusion pressure and a rise in heart rate may outweigh the benefits of improved myocardial blood flow so that further ischaemia ensues.

• Miscellaneousagranulocytosis has been reported.

Kinetics

While enoximone is well absorbed from the gut an extensive first-pass metabolism renders it useless when given orally. About 70% is plasma protein-bound and

metabolism occurs in the liver to a renally excreted active sulphoxide metabolite with 10% of the activity of enoximone and a terminal half-life of 7.5 hours. Only small amounts are excreted unchanged in the urine and by infusion enoximone has a terminal half-life of 4.5 hours. It has a wide therapeutic ratio and the risks of toxicity are low. The dose should be reduced in renal failure.

Milrinone

Milrinone is a bipyridine derivative and a selective phosphodiesterase III inhibitor with similar effects to enoximone. However, it has been associated with an increased mortality rate when administered orally to patients with severe heart failure.

Preparation and Uses

Milrinone is formulated as a yellow solution containing 1 mg.ml1 and may be stored at room temperature. It should be diluted before administration and should only be used intravenously for the short-term management of cardiac failure.

Kinetics

Approximately 70% is plasma protein-bound. It has an elimination half-life of 12.5 hours and is 80% excreted in the urine unchanged. The dose should be reduced in renal failure.

Amrinone

Amrinone is not available in the UK. It has a similar pharmacological profile to the other selective phosphodiesterase inhibitors. Approximately 40% is excreted unchanged in the urine. One in 40 patients suffers a reversible dose-related thrombocytopenia.

Glucagon

a cells within the pancreas secrete the polypeptide glucagon. The activation of glucagon receptors, via G protein mediated mechanisms, stimulates adenylate cyclase and increases intracellular cAMP. It has only a limited role in cardiac failure, occasionally being used in the treatment of b-blocker overdose by an initial bolus of 10 mg followed by infusion of up to 5 mg.hr1. Hyperglycaemia and hyperkalaemia may complicate its use.

Ca2+

While intravenously administered Ca2+ salts often improve blood pressure for a few minutes, their use should be restricted to circulatory collapse due to hyperkalaemia and Ca2+ channel antagonist overdose.

T3

Thyroxine (T4) and triiodothyronine (T3) have positive inotropic and chronotropic effects via intracellular mechanisms. They are only used to treat hypothyroidism and are discussed in more detail in Chapter 24.

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13
Adrenoreceptor Antagonists

- a-Adrenoreceptor antagonists
- b-Adrenoreceptor antagonists
- Combined a- and b-adrenoreceptor antagonists

a-Adrenoreceptor Antagonists

a-Adrenoreceptor antagonists (a-blockers) prevent the actions of sympathomimetic agents on a-adrenoreceptors. Certain a-blockers (phentolamine, phenoxybenzamine) are non-specific and inhibit both a1- and a2-receptors, while others selectively inhibit a1-receptors (prazosin) or a2-receptors (yohimbine). The actions of specific a adrenoreceptor stimulation are shown in Table 13.1.

Non-selective a *Blockade:*
Phentolamine

Phentolamine (an imidazolone) is a competitive non-selective a-blocker. Its affinity for a1-adrenoreceptors is three times that for a2-adrenoreceptors.

Table 13.1: Actions of specific a-adrenoreceptor stimulation.

Receptor type	Action
Post-synaptic	
a1-Receptors	vasoconstriction
	mydriasis
	contraction of bladder sphincter
a2-Receptors	platelet aggregation
	hyperpolarization of some CNS neurones
Presynaptic	
a2-Receptors	inhibit noradrenaline release

Presentation

It is presented as 10 mg phentolamine mesylate in 1 ml clear pale yellow solution. The intravenous dose is 15 mg and should be titrated to effect. The onset of action is 12 minutes and its duration of action is 520 minutes.

Uses

Phentolamine is used in the treatment of hypertensive crises due to excessive sympathomimetics, monoamine oxidase inhibitor (MAOI) reactions with tyramine and phaeochromocytoma, especially during tumour manipulation. It has a role in the assessment of sympathetically mediated chronic pain and has previously been used to treat pulmonary hypertension. Injection into the corpus cavernosum has been used to treat impotence due to erectile failure.

Effects

- Cardiovasculara1 blockade results in vasodilatation and hypotension while a2 blockade facilitates noradrenaline release leading to tachycardia and a raised cardiac output. Pulmonary artery pressure is also reduced. Vasodilatation of vessels in the nasal mucosa leads to marked nasal congestion.

- Respiratorythe presence of sulphites in phentolamine ampoules may lead to hypersensitivity reactions, which are manifest as acute bronchospasm in susceptible asthmatics.

- Gutphentolamine increases secretions and motility of the gastrointestinal tract.

- Metabolicit may precipitate hypoglycaemia secondary to increased insulin secretion.

Kinetics

The oral route is rarely used and has a bioavailability of 20%. It is 50% plasma protein-bound and extensively metabolized, leaving about 10% to be excreted unchanged in the urine. Its elimination half-life is 20 minutes.

Phenoxybenzamine

Phenoxybenzamine is a long-acting non-selective a-blocker. It has a high affinity for a1-adrenoreceptors.

Presentation

It is presented as capsules containing 10 mg and as a clear, faintly straw coloured solution for injection containing 100 mg/2 ml phenoxybenzamine hydrochloride with ethyl alcohol, hydrochloric acid and propylene glycol.

Uses

Phenoxybenzamine is used in the preoperative management of phaeochromocytoma (to allow expansion of the intravascular compartment), peri-operative management of some neonates undergoing cardiac surgery, hypertensive crises and occasionally as an adjunct to the treatment of severe shock. The oral dose starts at 10 mg and is increased daily until hypertension is controlled, the usual dose is 12 mg.kg1.day1. Intravenous administration should be via a central cannula and the usual dose is 1 mg.kg1.day1 given as a slow infusion in at least 200 ml 0.9% saline. b-blockade may be required to limit reflex tachycardia.

Mechanism of Action

Its effects are mediated by a reactive intermediate that forms a covalent bond to the a-adrenoreceptor resulting in irreversible blockade. In addition to receptor blockade, phenoxybenzamine inhibits neuronal and extra-neuronal uptake of catecholamines.

Effects

• Cardiovascularhypotension, which may be orthostatic, and reflex tachycardia are characteristic. Overdose should be treated with noradrenaline. Adrenaline will lead to unopposed b effects thereby compounding the hypotension and tachycardia. There is an increase in cardiac output and blood flow to skin, viscera and nasal mucosa leading to nasal congestion.

• Central nervous systemit usually causes marked sedation although convulsions have been reported after rapid intravenous infusion. Meiosis is also seen.

• Miscellaneousimpotence, contact dermatitis.

Kinetics

Phenoxybenzamine is incompletely and variably absorbed from the gut (oral bioavailability about 25%). Its maximum effect is seen at 1 hour following an intravenous dose. The plasma half-life is about 24 hours and its effects may persist for 3 days while new a-adrenoreceptors are synthesized. It is metabolized in the liver and excreted in urine and bile.

Selective a*1 Blockade:*
Prazosin

Prazosin (a quinazoline derivative) is a highly selective a1-adrenoreceptor antagonist.

Presentation and Uses

Prazosin is available as 0.52 mg tablets. It is used in the treatment of essential hypertension, congestive heart failure, Raynaud's syndrome and benign prostatic hypertrophy. The initial dose is 0.5 mg tds, which may be increased to 20 mg.day1.

Effects

• Cardiovascularprazosin produces vasodilatation of arteries and veins and a reduction of systemic vascular resistance with little or no reflex tachycardia. Diastolic pressures fall the most. Severe postural hypotension and syncope may follow the first dose. Cardiac output may increase in those with heart failure secondary to reduced filling pressures.

• Urinaryit relaxes the bladder trigone and sphincter muscle thereby improving urine flow in those with benign prostatic hypertrophy. Impotence and priapism have been reported.

• Central nervous systemfatigue, headache, vertigo and nausea all decrease with continued use.

• Miscellaneousit may produce a false-positive when screening urine for metabolites of noradrenaline (VMA and MHPG seen in phaeochromocytoma).

Kinetics

Plasma levels peak about 90 minutes following an oral dose with a variable oral bioavailability of 5080%. It is highly protein-bound mainly to albumin, and is extensively metabolized in the liver by demethylation and conjugation. Some of the metabolites are active. It has a plasma half-life of 3 hours. It may be used safely in patients with renal impairment as it is largely excreted in the bile.

Selective a*2 Blockade:*
Yohimbine

The principal alkaloid of the bark of the yohimbe tree is formulated as the hydrochloride and has been used in the treatment of impotence. It has a variable effect on the cardiovascular system resulting in a raised heart rate and blood pressure but may precipitate orthostatic hypotension. *In vitro* it blocks the hypotensive responses of clonidine. It has an antidiuretic effect, and can cause anxiety and manic reactions. It is contraindicated in renal or hepatic disease.

b-Adrenoreceptor Antagonists

b-Adrenoreceptor antagonists (b-blockers) are widely used in the treatment of hypertension, angina and peri-myocardial infarction.

They are also used in patients with phaeochromocytoma (preventing the reflex tachycardia associated with a-blockade), hyperthyroidism (propranolol), hypertrophic obstructive cardiomyopathy (to control infundibular spasm), anxiety associated with high levels of catecholamines, topically in glaucoma, in the prophylaxis of migraine and to suppress the response to laryngoscopy and at extubation (esmolol).

They are all competitive antagonists with varying degrees of receptor selectivity. In addition some have intrinsic sympathomimetic activity (i.e. are partial agonists; cf. p34) while others demonstrate membrane stabilizing activity. These three features form the basis of their differing pharmacological profiles. Prolonged administration may result in an increase in the number of b-adrenoreceptors.

Receptor Selectivity

In suitable patients, the useful effects of b-blockers are mediated via antagonism of b1-adrenoreceptors, while antagonism of b2-adrenoreceptors results in unwanted effects. Atenolol, esmolol and metoprolol demonstrate b1-adrenoreceptor selectivity (cardioselectivity) although when given in high dose b2-antagonism may also be seen. All b-blockers should be used with extreme caution in patients with poor ventricular function as they may precipitate serious cardiac failure.

Intrinsic Sympathomimetic ActivityPartial Agonist Activity

Partial agonists are drugs that are unable to elicit the same maximum response as a full agonist despite adequate receptor affinity. In theory, b-blockers with partial agonist activity will produce sympathomimetic effects when circulating levels of catecholamines are low, while producing antagonist effects when sympathetic tone is high. In patients with mild cardiac failure they should be less likely to induce

Table 13.2: Comparison between receptor selectivity, intrinsic sympathomimetic activity and membrane stabilizing activity of various b-blockers.

	b1-Receptor selectivity-cardioselectivity	Intrinsic sympathomimetic activity	Membrane stabilizing activity
Acebutolol	+	+	+
Atenolol	+ +		
Esmolol	+ +		
Metoprolol	+ +		+
Oxprenolol		+	+
Pindolol		+ +	+
Propranolol			+ +
Sotalol			
Timolol		+	+
Labetalol		±	+

bradycardia and heart failure. However, they should not be used in those with more severe heart failure as b-blockade will further reduce cardiac output.

Membrane Stabilizing Activity

These effects are probably of little clinical significance as the doses required to elicit them are higher than those seen in vivo.

Effects

• Cardiacb-blockers have negative inotropic and chronotropic properties on cardiac muscle; sino-atrial (SA) node automaticity is decreased and atrio-ventricular (AV) node conduction time is prolonged leading to a bradycardia, while contractility is also reduced. The bradycardia lengthens the coronary artery perfusion time (during diastole) thereby increasing oxygen supply while reduced contractility diminishes oxygen demand. These effects are more important than those that tend to compromise the supply/demand equation, i.e. prolonged systolic ejection time, dilation of the ventricles and increased coronary vascular resistance (due to antagonism of the vasodilatory b2 coronary receptors). The improvement in the balance of oxygen supply/demand forms the basis for their use in angina and peri-myocardial infarction. However, in patients with poor left ventricular function b-blockade may lead to cardiac failure. b-blockers are class II antiarrhythmic agents and are mainly used to treat arrhythmias associated with high levels of catecholamines (see Chapter 14).

• Circulatorythe mechanism by which b-blockers control blood pressure is not yet fully elucidated but probably includes a reduced heart rate and cardiac output, and inhibition of the renin-angiotensin system. Inhibition of b1-receptors at the juxtaglomerular apparatus reduces renin release leading ultimately to a reduction in angiotensin II and its effects (vasoconstriction and augmenting aldosterone production). In addition, the baroreceptors may be set at a lower level, presynaptic b2-receptors may inhibit noradrenaline release and some b-blockers may have central effects. However, due to antagonism of peripheral b2-receptors there will be an element of vasoconstriction, which appears to have little hypertensive effect but does result in poor peripheral circulation and cold hands.

• Respiratoryall b-blockers given in sufficient dose will precipitate bronchospasm via b2-antagonism. The relatively cardioselective drugs (atenolol, esmolol and metoprolol) are preferred but should still be used with extreme caution in patients with asthma.

• Metabolicthe control of blood sugar is complicated involving different tissue types (liver, pancreas, adipose), receptors (a-, b-adrenoreceptors)

and hormones (insulin, glucagon, catecholamines). Non-selective b-blockade may obtund the normal blood sugar response to exercise and hypoglycaemia although it may also increase the resting blood sugar levels in diabetics with hypertension. Therefore, non-selective b-blockers should not be used with hypoglycaemic agents. In addition, b-blockade may mask the normal symptoms of hypoglycaemia. Lipid metabolism may be altered resulting in increased triglycerides and reduced high density lipoproteins.

• Central nervous systemthe more lipid soluble b-blockers (metoprolol, propranolol) are more likely to produce CNS side-effects. These include depression, hallucination, nightmares, paranoia and fatigue.

• Occularintra-occular pressure is reduced, probably as a result of decreased production of aqueous humour.

• Gutdry mouth and gastrointestinal disturbances.

Kinetics

Varying lipid solubility confers the main differences seen in the kinetics of b-blockers. Those with low lipid solubility (atenolol) are poorly absorbed from the gut, undergo little hepatic metabolism and are excreted largely unchanged in the urine. However, those with high lipid solubility are well absorbed from the gut and are extensively metabolized in the liver. They have a shorter half-life and consequently need more frequent administration. In addition, they cross the bloodbrain barrier resulting in sedation and nightmares. Protein binding is variable.

Individual b-*Blockers:*
Acebutolol

Acebutolol is a relatively cardioselective b-blocker that is only available orally. It has limited intrinsic sympathomimetic activity and some membrane stabilizing properties. The adult dose is 400 mg bd but may be increased to 1.2 g.day1 if required.

Kinetics

Acebutolol is well absorbed from the gut due to its moderately high lipid solubility, but due to a high first-pass metabolism its oral bioavailability is only 40%. Despite its lipid solubility it does not cross the bloodbrain barrier to any great extent. Hepatic metabolism produces the active metabolite diacetol, which has a longer half-life, and is less cardioselective than acebutolol. Both are excreted in bile and may undergo enterohepatic recycling. They are also excreted in urine and the dose should be reduced in the presence of renal impairment.

Atenolol

Atenolol is a relatively cardioselective b-blocker that is available as 25100 mg tablets, a syrup containing 5 mg.ml1 and as a colourless solution for intravenous use containing 5 mg/10 ml. The oral dose is 50100 mg.day1 while the intravenous dose is 2.5 mg slowly, repeated up to a maximum of 10 mg, which may then be followed by an infusion.

Kinetics

Atenolol is incompletely absorbed from the gut. It is not significantly metabolized and has an oral bioavailability of 45%. Only 5% is protein-bound. It is excreted unchanged in the urine and, therefore, the dose should be reduced in patients with renal impairment. It has an elimination half-life of 7 hours but its actions appear to persist for longer than this would suggest.

Esmolol

Esmolol is a highly lipophilic, cardioselective b-blocker with a rapid onset and offset. It is presented as a clear liquid with either 2.5 g or 100 mg in 10 ml. The former should be diluted before administration as an infusion (dose range 50200 µg.kg1.min1), while the latter is titrated in 10 mg boluses to effect. It is used in the short-term management of tachycardia and hypertension in the perioperative period, and for acute supraventricular tachycardia. It has no intrinsic sympathomimetic activity or membrane stabilizing properties.

Kinetics

Esmolol is only available intravenously and is 60% protein-bound. Its volume of distribution is 3.5 l.kg1. It is rapidly metabolized by red blood cell esterases to an essentially inactive acid metabolite (with a long half-life) and methyl alcohol. Its rapid metabolism ensures a short half-life of 10 minutes. The esterases responsible for its hydrolysis are distinct from plasma cholinesterase so that it does not prolong the actions of suxamethonium.

Like other b-blockers it may also precipitate heart failure and bronchospasm, although its short duration of action limits these side-effects.

It is irritant to veins and extravasation may lead to tissue necrosis.

Metoprolol

Metoprolol is a relatively cardioselective b-blocker with no intrinsic sympathomimetic activity. Early use of metoprolol in myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. It is also used in hypertension, as an adjunct in thyrotoxicosis and for migraine prophylaxis. The dose is 50200 mg daily. Up to 5 mg may be given intravenously for arrhythmias and in myocardial infarction.

Kinetics

Absorption is rapid and complete but due to hepatic first-pass metabolism its oral bioavailability is only 50%. However, this increases to 70% during continuous administration and is also increased when given with food. Hepatic metabolism may exhibit genetic polymorphism resulting in two different half-life profiles, of 3 and 7 hours. Its high lipid solubility enables it to cross the bloodbrain barrier and also into breast milk. Only 20% is plasma protein-bound.

Propranolol

Propranolol is a non-selective b-blocker without intrinsic sympathomimetic activity. It exhibits the full range of effects described above at therapeutic concentrations. It is a racemic mixture, the S-isomer conferring most of its effects, although the R-isomer is responsible for preventing the peripheral conversion of T4 to T3.

Uses

Propranolol is used to treat hypertension, angina, essential tremor and in the prophylaxis of migraine. It is the b-blocker of choice in thyrotoxicosis as it not only inhibits the effects of the thyroid hormones, but also prevents the peripheral conversion of T4 to T3. Intravenous doses of 0.5 mg (up to 10 mg) are titrated to effect. The oral dose ranges from 160320 mg daily but due to increased clearance in thyrotoxicosis even higher doses may be required.

Kinetics

Owing to its high lipid solubility it is well absorbed from the gut but a high first-pass metabolism reduces its oral bioavailability to 30%. It is highly protein-bound although this may be reduced by heparin. Hepatic metabolism of the R-isomer is more rapid than the S-isomer and one of their metabolites, 4-hydroxypropranolol, retains some activity. Its elimination is dependent on hepatic metabolism but is impaired in renal failure by an unknown mechanism. The duration of action is longer than its half-life of 4 hours would suggest.

Sotalol

Sotalol is a non-selective b-blocker with no intrinsic sympathomimetic properties. It also has class III antiarrhythmic properties (see Chapter 14).

It is a racemic mixture, the D-isomer conferring the class III activity while the Lisomer has both class III and class II (b-blocking) actions.

Uses

Sotalol is used to treat ventricular tachyarrhythmias and for the prophylaxis of paroxysmal supraventricular tachycardias following DC cardioversion. The ventricular rate is also well controlled if sinus rhythm degenerates back into atrial

fibrillation. The CSM states that sotalol should not be used for angina, hypertension, thyrotoxicosis or peri-myocardial infarction. The oral dose is 80160 mg bd and the intravenous dose is 50100 mg over 20 minutes.

Other Effects

The most serious side-effect is precipitation of torsades de pointes which is rare, occurring in less than 2% of those being treated for sustained ventricular tachycardia or fibrillation. It is more common with higher doses, a prolonged QT interval and electrolyte imbalance. It may precipitate heart failure.

Kinetics

Sotalol is completely absorbed from the gut and its oral bioavailability exceeds 90%. It is not protein-bound or metabolized. Approximately 90% is excreted unchanged in urine while the remainder is excreted in bile. Renal impairment significantly reduces clearance.

Combined a- and b-Adrenoreceptor Antagonists

Labetalol

Labetalol, as its name indicates, is an a- and b-adrenoreceptor antagonist. The a-blockade is specific to a1-receptors while b-blockade is non-specific. It contains two asymmetric centres and exists as a mixture of four stereoisomers present in equal proportions. The (SR)-stereoisomer is probably responsible for the a1 effects while the (RR)-stereoisomer probably confers the b-blockade. The ratio of a1:b blocking effects is dependent on the route of administration: 1:3 for oral, 1:7 for intravenous.

Presentation and Uses

Labetalol is available as 50400 mg tablets and as a colourless solution containing 5 mg.ml1. It is used to treat hypertensive crises and to facilitate hypotension during anaesthesia. The intravenous dose is 520 mg titrated up to a maximum of 200 mg. The oral form is used to treat hypertension associated with angina and during pregnancy where the dose is 100800 mg bd but may be increased to a maximum of 2.4 g daily.

Mechanism of Action

Selective a1-blockade produces peripheral vasodilatation while b-blockade prevents reflex tachycardia. Myocardial afterload and oxygen demand are decreased providing favourable conditions for those with angina.

Kinetics

Labetalol is well absorbed from the gut but due to an extensive hepatic first-pass metabolism its oral bioavailability is only 25%. However, this may increase markedly with increasing age and when administered with food. It is 50% protein-bound. Metabolism occurs in the liver and produces several inactive conjugates.

Table 13.3: Various pharmacological properties of some b-blockers.

Drug	Lipid solubility	Absorption (%)	Bioavailability (%)	Protein binding (%)	Elimination half-life (h)	Clearance	Active metabolites
Acebutolol	+ +	90	40	25	6	hepatic metabolism and renal excretion	yes
Atenolol	+	45	45	5	7	renal	no
Esmolol	+ + +	n/a	n/a	60	0.15	plasma hydrolysis	no
Metoprolol	+ + +	95	50	20	37*	hepatic metabolism	no
Oxprenolol	+ + +	80	40	80	2	hepatic metabolism	no
Pindolol	+ +	90	90	50	4	hepatic metabolism	no
Propranolol	+ + +	90	30	90	4	hepatic metabolism	yes
Sotalol	+	85	85	0	15	renal	no
Timolol	+ + +	90	50	10	4	hepatic metabolism and renal excretion	no
Labetalol	+ + +	70	25	50	5	hepatic metabolism	no

*Depends on genetic polymorphismmay be fast or slow hydroxylators.

14
Anti-Arrhythmics

Physiology

Cardiac Action Potential

The heart is composed of pacemaker, conducting and contractile tissue. Each has a different action potential morphology allowing the heart to function as a coordinated unit.

The sino-atrial (SA) node is in the right atrium, and of all cardiac tissue it has the fastest rate of spontaneous depolarization so that it sets the heart rate. The slow spontaneous depolarization (pre-potential or pacemaker potential) of the membrane potential is due to increased Ca2+ conductance (directed inward). At 40 mV, slow voltage-gated Ca2+ channels (L channels) open resulting in membrane depolarization. Na+ conductance changes very little. Repolarization is due to increased K+ conductance, while Ca2+ channels close (Figure 14.1a).

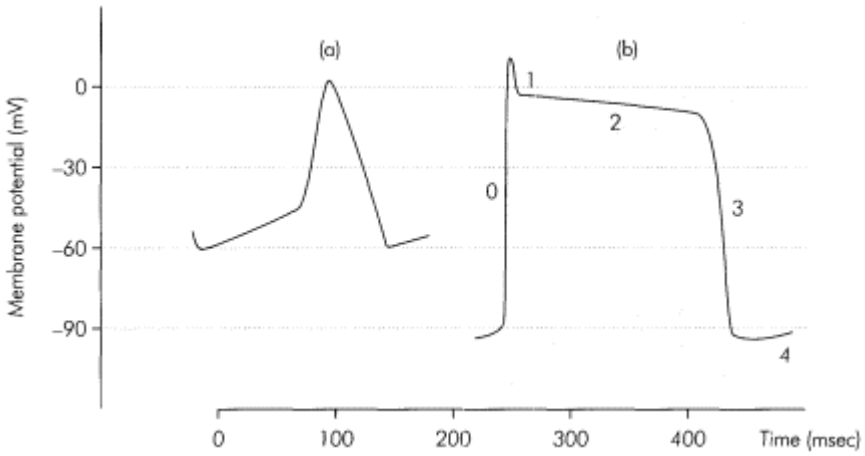


Figure 14.1:
Action potentials of (a) pacemaker and (b) contractile tissue.

Contractile cardiac tissue has a more stable resting potential at 80 mV. Its action potential has been divided into five phases (Figure 14.1b):

• Phase 0describes the rapid depolarization (duration < 1 ms) of the membrane, resulting from increased Na+ (and possibly some Ca2+) conductance through voltage-gated Na+ channels.

• Phase 1represents closure of the Na+ channels while Cl is expelled.

• Plateau phase 2due to Ca2+ influx via voltage sensitive type-L Ca2+ channels and lasts up to 150 ms. This period is also known as the absolute refractory period in which the myocyte cannot be further depolarized. This prevents myocardial tetany.

• Phase 3commences when the Ca2+ channels are inactivated and there is an increase in K+ conductance that returns the membrane potential to its resting value. This period is also known as the relative refractory period in which the myocyte requires a greater than normal stimulus to provoke a contraction.

• Phase 4during this the Na+/K+ ATPase maintains the ionic concentration gradient at about 80 mV, although there will be variable spontaneous 'diastolic' depolarization.

Arrhythmias

Tachyarrhythmias

• These may originate from enhanced automaticity where the resting potential of contractile tissue looses its stability and may reach its threshold for depolarization before that of the SA node. This is seen during ischaemia and hypokalaemia.

• Ischaemic myocardium may result in oscillations of the membrane potential. These after-potentials may reach the threshold potential and precipitate tachyarrhythmias.

• Re-entry or circus mechanisms describe how an ectopic focus may originate, leading to tachyarrhythmias (Figure 14.2).

Bradyarrhythmias

These are due to failure of conduction from the SA node to surrounding tissue. Second- and third-degree block becomes clinically significant. Atropine, b stimulation or pacing may be required.

Classification of Anti-Arrhythmics

Traditionally anti-arrhythmics have been classified according to the VaughanWilliams classification despite its failure to include digoxin and more

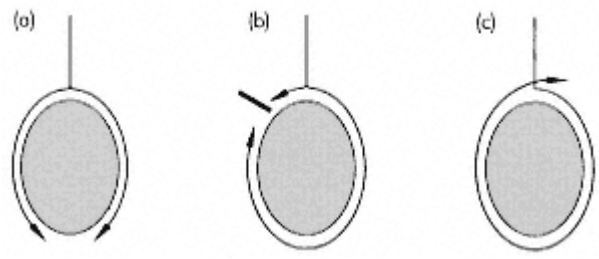


Figure 14.2:
Generating a re-entrant or circus arrhythmia. The atrioventricular (AV) node, terminal Purkinje fibres and ischaemic myocardium may each contain alternative pathways for membrane depolarization. Normally the impulse is terminated in the muscle fibre (a); however, if conduction in one of the alternative limbs is delayed (b) it may be neutralized by retrograde conduction in the other limb. When conduction is delayed to the extent that the refractory period has been passed, conduction may continue in a retrograde manner and then complete the circuit so that it becomes self-perpetuating (c).

recently introduced drugs such as adenosine. In addition, individual agents do not fall neatly into one category, e.g. sotalol has class I, II and III activity (Table 14.2).

Table 14.1: VaughanWilliams classification.

Class	Mechanism	Drugs
Ia	Na+ channel blockadeprolongs the refractory period of cardiac muscle	quinidine, procainamide, disopyramide
Ib	Na+ channel blockadeshortens the refractory period of cardiac muscle	lignocaine, mexiletine, phenytoin
Ic	Na+ channel blockadeno effect on the refractory period of cardiac muscle	flecainide, propafenone
II	b-Adrenoreceptor blockade	propranolol, atenolol, esmolol
III	K+ channel blockade	amiodarone, bretylium, sotalol
IV	Ca2+ channel blockade	verapamil, diltiazem

Anti-arrhythmics may also be divided on the basis of their clinical use in the treatment of

- Supraventricular tachyarrhythmias (SVT) (digoxin, adenosine, verapamil, b-blockers, quinidine)
- Ventricular tachyarrhythmias (VT) (lignocaine, mexiletine)
- Both SVT and VT (amiodarone, flecainide, procainamide, disopyramide, propafenone, sotalol)
- Digoxin toxicity (phenytoin)

Supraventricular Tachyarrhythmias

Digoxin

Presentation

Digoxin is a glycoside that is extracted from the leaves of the foxglove (*Digitalis lanata*) and is available as oral (tablets of 62.5250 µg, elixir 50 µg.ml1) and intravenous (100250 µg.ml1) preparations. The intramuscular route is associated with variable absorption, pain and tissue necrosis.

Uses

Digoxin is widely used in the treatment of atrial fibrillation and atrial flutter. It has been used in heart failure but the initial effects on cardiac output may not be sustained and other agents may produce a better outcome. It has only minimal activity on the normal heart. It should be avoided in patients with ventricular extrasystoles or ventricular tachycardia (VT) as it may precipitate ventricular fibrillation (VF) due to increased cardiac excitability.

Treatment starts with the administration of a loading dose of between 1.0 and 1.5 mg in divided doses over 24 hours followed by a maintenance dose of 125500 µg per day. The therapeutic range is 12 µg.l1.

Mechanism of Action

Digoxin has direct and indirect actions on the heart.

• Directit binds to and inhibits cardiac Na+/K+ ATPase leading to increased intracellular Na+ and decreased intracellular K+ concentrations. The raised intracellular Na+ concentration leads to an increased exchange with extracellular Ca2+ resulting in increased availability of intracellular Ca2+, which has a positive inotropic effect, increasing excitability and force of contraction. The refractory period of the AV node and the bundle of His is increased and the conductivity reduced.

• Indirectthe release of acetylcholine at cardiac muscarinic receptors is enhanced. This slows conduction and further prolongs the refractory period in the AV node and the bundle of His.

In atrial fibrillation the atrial rate is too high to allow a 1:1 ventricular response. By slowing conduction through the AV node the rate of ventricular response is reduced. This allows for a longer period of coronary blood flow and a greater degree of ventricular filling so that cardiac output is increased.

Side-Effects

Digoxin has a low therapeutic ratio and side-effects are not uncommon:

• Cardiacthese include various arrhythmias and conduction disturbancespremature ventricular contractions, bigemini, all forms of AV

block including third-degree block, junctional rhythm and atrial or ventricular tachycardia. Hypokalaemia, hypercalcaemia or altered pH may precipitate side-effects. The ECG signs of prolonged PR interval, characteristic ST segment depression, T wave flattening and shortened QT interval are not signs of toxicity.

DC cardioversionsevere ventricular arrhythmias may be precipitated in patients with toxic levels and it is recommended to withhold digoxin for 24 hours before elective cardioversion.

• Non-cardiacanorexia, nausea and vomiting, diarrhoea and lethargy. Visual disturbances (including deranged redgreen colour perception) and headache are common while gynaecomastia occurs during longterm administration. Skin rashes are rarely seen and may be accompanied by an eosinophilia.

• Interactionsplasma levels are increased by amiodarone, captopril, erythromycin and carbenoxolone. They are reduced by antacids, cholestyramine, phenytoin and metoclopramide. Ca2+ channel antagonists produce variable effects, verapamil will increase, while nifedipine and diltiazem may have no effect or produce a small rise in plasma levels.

Kinetics

The absorption of digoxin from the gut is variable depending on the specific formulation used, but the oral bioavailability is greater than 70%. It is about 25% plasma protein-bound and has a volume of distribution of 510 l.kg1. Its volume of distribution is significantly increased in thyrotoxicosis and decreased in hypothyroidism. It undergoes only minimal hepatic metabolism, being excreted mainly in the unchanged form by filtration at the glomerulus and active tubular secretion. The elimination half-life is approximately 35 hours but is increased significantly in the presence of renal failure.

Toxicity

Plasma concentrations exceeding 2.5 µg.l1 are associated with toxicity although serious problems are unusual at levels below 10 µg.l1. Despite these figures the severity of toxicity does not correlate well with plasma levels. However, a dose of more than 30 mg is invariably associated with death unless digoxin-specific antibody fragments (Fab) are used.

Treatment of Digoxin Toxicity

Gastric lavage should be used with caution as any increase in vagal tone may precipitate further bradycardia or cardiac arrest. Owing to Na+/K+ ATPase inhibition, hyperkalaemia may be a feature and should be corrected. Hypokalaemia will exacerbate cardiac toxicity and should also be corrected. Where bradycardia is symptomatic atropine or pacing is preferred to infusions of catecholamines, which may

precipitate further arrhythmias. Ventricular arrhythmias may be treated with lignocaine or phenytoin.

If plasma levels rise above 20 µg.l1, there are life-threatening arrhythmias or hyperkalaemia becomes uncontrolled, digoxin-specific Fab are indicated. These are IgG fragments. Digoxin is bound more avidly by Fab than by its receptor so that it is effectively removed from its site of action. The inactive digoxinFab complex is removed from the circulation by the kidneys. There is a danger of hypersensitivity or anaphylaxis on re-exposure.

Adenosine

Adenosine is a naturally occurring purine nucleoside consisting of adenine (the purine base) and D-ribose (the pentose sugar), which is present in all cells.

Presentation

Adenosine is presented as a colourless solution in vials containing 3 mg.ml1. It should be stored at room temperature.

Uses

Adenosine is used to differentiate between SVT, where the rate is at least transiently slowed and VT, where the rate does not slow. Where SVT is due to re-entry circuits that involve the AV node adenosine may covert the rhythm to sinus. Atrial fibrillation and flutter are not converted by adenosine to sinus rhythm as they are not generated by re-entry circuits involving the AV node, although its use in this setting will slow the ventricular response and aid ECG diagnosis.

Mechanism of Action

Adenosine has specific actions on the SA and AV node mediated by adenosine A1 receptors that are not found elsewhere within the heart. These adenosine sensitive K+ channels are opened, causing membrane hyperpolarization, and Gi-linked proteins cause a reduction in cAMP. This results in a dramatic negative chronotropic effect within the AV node.

Side-Effects

Owing to its short half-life its side-effects are also short lived but may be very distressing.

• Cardiacit may induce atrial fibrillation or flutter as it decreases the atrial refractory period. It is contraindicated in those with second- or third-degree AV block or with sick sinus syndrome.

• Non-cardiacthese include chest discomfort, shortness of breath and facial flushing. It should be used with caution in asthmatics as it may precipitate bronchospasm.

• Drug interactionsits effects may be enhanced by dipyridamole (by blocking its uptake) and antagonized by the methylxanthines especially aminophylline.

Kinetics

Adenosine is given in incremental doses from 3 to 12 mg as an intravenous bolus, preferably via a central cannula. It is rapidly de-aminated in the plasma and taken up by red blood cells so that its half-life is less than 10 seconds.

Verapamil

Verapamil is a competitive Ca2+ channel antagonist.

Presentation

It is presented as film-coated and modified-release tablets and as a solution for intravenous injection containing 2.5 mg.ml1

Uses

Verapamil is used to treat SVT, atrial fibrillation or flutter, which it may slow or convert to a sinus rhythm. It is also used in the prophylaxis of angina and the treatment of hypertension.

Mechanism of Action

Verapamil prevents the influx of Ca2+ through voltage-sensitive slow (L) channels in the SA and AV node, thereby reducing their automaticity. It has a much less marked effect on the contractile tissue of the heart, but does reduce Ca2+ influx during the plateau phase 2. Antagonism of these Ca2+ channels results in a reduced rate of conduction through the AV node and coronary artery dilatation.

Side-Effects

• Cardiacif used to treat SVT complicating WolffParkinsonWhite (WPW) syndrome, verapamil may precipitate VT due to increased conduction across the accessory pathway. In patients with poor left ventricular function it may precipitate cardiac failure. When administered concurrently with agents that also slow AV conduction (digoxin, b-blockers, halothane) it may precipitate serious bradycardia and AV block. It may increase the serum levels of digoxin. Grapefruit juice has been reported to increase serum levels and should be avoided during verapamil therapy.

Although its effects are relatively specific to cardiac tissue it may also precipitate hypotension through vascular smooth muscle relaxation.

- Non-cardiaccerebral artery vasodilatation occurs after the administration of verapamil.

Kinetics

Verapamil is used orally and intravenously. While almost 90% is absorbed from the gut a high first-pass metabolism reduces its oral bioavailability to about 25%. Approximately 90% is bound to plasma proteins. It is metabolized in the liver to at least 12 inactive metabolites that are excreted in the urine. Its volume of distribution is 35 1.kg1. The elimination half-life of 37 hours is prolonged with higher doses as hepatic enzymes become saturated.

b-*Blockers*

b-Blockers antagonize the effects of catecholamines. Therefore, they induce a bradycardia (by prolonging 'diastolic' depolarizationphase 4), depress myocardial contractility and prolong AV conduction. In addition, some b-blockers exhibit a degree of membrane stabilizing activity (class I) although this probably has little clinical significance. Sotalol also demonstrates class III activity by blocking K+ channels and prolonging repolarization.

b-Blockers are used in the treatment of hypertension, angina, myocardial infarction, tachyarrhythmias, thyrotoxicosis, anxiety states, the prophylaxis of migraine and topically in glaucoma. Their use as an anti-arrhythmic is limited to treatment of paroxysmal SVT and sinus tachycardia due to increased levels of catecholamines. They have a role following acute myocardial infarction where they may reduce arrhythmias and prevent further infarction. Owing to their negative inotropic effects they should be avoided in those with poor ventricular function for fear of precipitating cardiac failure.

Esmolol

Esmolol is a relatively cardioselective b-blocker with a rapid onset and offset.

Presentation

It is presented as a clear liquid with either 2.5 g or 100 mg in 10 ml. The former should be diluted before administration as an infusion (dose range 50200 µg.kg1.min1), while the latter is titrated in 10 mg boluses to effect.

Uses

Esmolol is used in the short-term management of tachycardia and hypertension in the peri-operative period, and for acute SVT. It has no intrinsic sympathomimetic activity or membrane-stabilizing properties.

Side-Effects

While esmolol is relatively cardioselective it does demonstrate b2 adrenoreceptor antagonism at high doses and should therefore be used with caution in asthmatics. Like other b-blockers it may also precipitate heart failure. However, due to its short duration of action these side-effects are also limited in time.

It is irritant to veins and extravasation may lead to tissue necrosis.

Kinetics

Esmolol is only available intravenously and is 60%, plasma protein-bound. Its volume of distribution is 3.5 l.kg1. It is rapidly metabolized by red blood cell esterases to an essentially inactive acid metabolite (with a long half-life) and methyl alcohol. Its rapid metabolism ensures a short half-life of 10 minutes. The esterases responsible for its hydrolysis are distinct from plasma cholinesterase so that it does not prolong the actions of suxamethonium.

Quinidine

The use of quinidine has declined as alternative treatments have become available with improved side-effect profiles. However, it may still be used to treat SVT including atrial fibrillation and flutter, and ventricular ectopic beats.

Mechanism of Action

Quinidine is a class Ia anti-arrhythmic and as such reduces the rate of rise of phase 0 of the action potential by blocking Na+ channels. In addition, it raises the threshold potential and prolongs the refractory period without affecting the duration of the action potential. It also antagonizes vagal tone.

Side-Effects

These are common and become unacceptable in up to 30% of patients.

• Cardiacquinidine may provoke other arrhythmias including heart block, sinus tachycardia (vagolytic action) and ventricular arrhythmias. The following ECG changes may be seen: prolonged PR interval, widened QRS and prolonged QT interval. When used to treat atrial fibrillation or flutter the patient should be pretreated with b-blockers, Ca2+ channel antagonists or digoxin to slow AV conduction, which may otherwise become enhanced leading to a ventricular rate equivalent to the atrial rate. Hypotension may result from a-blockade or direct myocardial depression, which is exacerbated by hyperkalaemia.

• Non-cardiaccentral nervous system toxicity known as 'cinchonism' is characterized by tinnitus, blurred vision, impaired hearing, headache and confusion.

• Drug interactionsdigoxin is displaced from its binding sites so that its serum concentration is increased. Phenytoin will reduce quinidine levels (hepatic enzyme induction) while cimetidine will increase quinidine levels (hepatic enzyme inhibition). The effects of depolarizing and non-depolarizing muscle relaxants are increased.

Kinetics

Quinidine is well absorbed from the gut and has an oral bioavailability of about 75%. It is highly protein-bound (about 90%) and is metabolized by the liver to active metabolites which are excreted mainly in the urine. The elimination half-life is 59 hours.

Ventricular Tachyarrhythmias

Lignocaine

Lignocaine is a class Ib anti-arrhythmic agent.

Presentation

The 1 or 2% solutions (1020 mg.ml1) are the preparations used in this setting.

Uses

Lignocaine is used to treat sustained ventricular tachyarrhythmias especially when associated with ischaemia (where inactivated Na+ channels predominate) or re-entry pathways. An initial intravenous bolus of 1 mg.kg1 is followed by an intravenous infusion of 13 mg.min1 for an adult. This infusion rate should be slowed where hepatic blood flow is reduced as hepatic metabolism will also be reduced.

Mechanism of Action

Lignocaine reduces the rate of rise of phase 0 of the action potential by blocking inactivated Na+ channels and raising the threshold potential. The duration of the action potential and the refractory period are decreased as the repolarization phase 3 is shortened.

Side-Effects

• Cardiaccardiovascular toxicity becomes apparent as plasma levels exceed 10 µg.ml1 and are manifest as AV block and unresponsive hypotension due to myocardial depression. Some of the cardiac effects may be due to central medullary depression.

• Non-cardiacthese become apparent only when the plasma levels exceed 4 µg.ml1. Initially central nervous system toxicity is manifest as circumoral tingling, dizziness and parasthesia. This progresses to confusion, coma and seizures as plasma levels rise above 5 µg.ml1.

Kinetics

When used for the treatment of arrhythmias lignocaine is only given intravenously. It is 33% unionized and 70% protein-bound. It is metabolized by hepatic amidases to products that are eliminated in the urine. Its elimination half-life is about 90 minutes so that in the presence of normal hepatic function a steady-state would be reached after about 6 hours in the absence of a loading dose. Its clearance is reduced in cardiac failure due to reduced hepatic blood flow.

Mexiletine

Mexiletine is an analogue of lignocaine with similar effects on ventricular tachyarrhythmias.

Presentation

It is presented as a colourless solution containing 250 mg mexiletine hydrochloride in 10 ml. The oral formulation is also available as modified release.

Uses

Mexiletine has similar indications to lignocaine particularly when arrhythmias are associated with ischaemia or digoxin.

Mechanism of Action

Mexiletine reduces the rate of rise of phase 0 of the action potential by blocking Na+ channels and raising the threshold potential. The duration of the action potential and the refractory period are decreased as the repolarization phase 3 is shortened.

Side-Effects

Mexiletine has a low therapeutic ratio and side-effects are common.

- Cardiacit may precipitate sinus bradycardia, supraventricular and ventricular tachyarrhythmias.

- Non-cardiacup to 40% of patients have unacceptable nausea and vomiting and altered bowel habit. Confusion, diplopia, seizures, tremor and ataxia are also seen. Thrombocytopenia, rash and jaundice have also been reported.

Kinetics

Its oral bioavailability of 90% reflects good absorption from the upper part of the small bowel and minimal first-pass metabolism (about 10%). It is 65% plasma protein-bound and has a volume of distribution of 613 l.kg1. It undergoes hepatic metabolism to a number of inactive metabolites. Up to 20% is excreted unchanged in the urine.

Both:
Supraventricular and Ventricular Tachyarrhythmias

Amiodarone

Amiodarone is a benzofuran derivative.

Presentation

It is presented as tablets containing 100200 mg and as a solution containing 150 mg per ampoule. It should be diluted in 5% dextrose before administration.

Uses

Amiodarone is used in the treatment of SVT, VT and WPW syndrome. It is a complex drug with many actions and side-effects.

A loading dose of 5 mg.kg1 over 1 hour followed by 15 mg.kg1 over 24 hours provides a starting point for its intravenous use, which should be adjusted according to response. When used orally treatment commences with 200 mg tds for 1 week, followed by 200 mg bd for a further week and thereafter 200 mg od.

Mechanism of Action

While it has been traditionally designated a class III anti-arrhythmic, amiodarone also demonstrates class I, II and IV activity. By blocking K+ channels it slows the rate of repolarization thereby increasing the duration of the action potential. The refractory period is also increased.

Side-Effects

The side-effects of amiodarone will affect most patients if given for long enough although most are reversible if treatment is stopped.

- Pulmonarypatients may develop a pneumonitis, fibrosis or pleuritis. The reported incidence is 10% at 3 years with a 10% mortality rate. However, if treatment is stopped early enough the process may be reversed. There is some evidence to suggest that a high FiO2 may be a risk factor in the development of acute pulmonary toxicity when amiodarone is used in critically ill patients.

- Thyroidboth hyper- and hypothyroidism have been observed and both are usually reversible.

- Hepaticcirrhosis, hepatitis and jaundice have all been observed. Liver function tests should be performed before and during long-term treatment.

- Cardiacwhen large doses are given rapidly it may cause bradycardia and hypotension. It has a low arrhythmic potential. The QT interval may be prolonged.

• Ophthalmiccorneal microdeposits occur commonly but have little clinical significance, causing visual haloes and some mild blurring of vision. They are reversible. Ophthalmic examination is recommended annually for those on long-term treatment.

• Gutduring the loading dose a metallic taste may be noticed. Minor intestinal upset is seen occasionally.

• Neurologicalperipheral neuropathy and rarely myopathy have been reported.

• Dermatologicalthe skin becomes photosensitive and may remain so for a number of months after finishing treatment. A slate-grey colour particularly of the face may develop.

• Interactionsthe effects of other highly protein-bound drugs (phenytoin, warfarin) are increased and their doses should be adjusted. The plasma level of digoxin may rise when amiodarone is added due to displacement from plasma protein binding sites, and cause signs of toxicity. Caution should be exercised when used with drugs that slow AV conduction (b-blockers, verapamil) and it should not be given with drugs that prolong the QT interval for fear of precipitating torsades de pointes.

• Miscellaneousthe intravenous preparation is irritant and should be administered via a central vein.

Kinetics

Amiodarone is poorly absorbed from the gut and has an oral bioavailability between 50 and 70%. In the plasma it is highly protein-bound (> 95%) and has a volume of distribution of 270 l.kg1. Muscle and fat accumulate amiodarone to a considerable extent. Its elimination half-life is long, varying from 20 to 100 days. Hepatic metabolism produces desmethylamiodarone, which appears to have some anti-arrhythmic activity.

Flecainide

Presentation

Flecainide is available orally or intravenously and is an amide local anaesthetic with class Ic properties. The oral dose is 100 mg bd (maximum 400 mg daily). When used intravenously the dose is 2 mg.kg1 over 1030 minutes (maximum 150 mg). This may then be followed by an infusion, initially at 1.5 mg.kg1.h1, which is then reduced to 100250 µg.kg1.h1 for up to 24 hours (maximum 24 hour dose is 600 mg).

Uses

Flecainide has powerful anti-arrhythmic effects against atrial and ventricular tachyarrhythmias including WPW syndrome.

Mechanism of Action

Flecainide prevents the fast Na+ flux into cardiac tissue and prolongs phase 0 of the action potential. It has no effect on the duration of the action potential or the refractory period. Its effects are particularly pronounced on the conducting pathways.

Side-Effects

• Cardiacflecainide may precipitate pre-existing conduction disorders and special care is required when used in patients with SA or AV disease or with bundle branch block. A paradoxical increase in ventricular rate may be seen in atrial fibrillation or flutter. When used to suppress ventricular ectopic beats following myocardial infarction it was associated with an increased mortality. Cardiac failure may complicate its use due to its negative inotropic effects. It raises the pacing threshold.

• Non-cardiacdizziness, parasthesia and headaches may complicate its use.

Kinetics

Flecainide is well absorbed from the gut and has an oral bioavailability of 90%. It is about 50% plasma protein-bound and has a volume of distribution of 610 l.kg1. Hepatic metabolism produces active metabolites, which along with unchanged drug are excreted in the urine.

Procainamide

Procainamide has similar effects to quinidine but is less vagolytic.

Uses

Procainamide has been used to treat both SVT and ventricular tachyarrhythmias. It is as effective as lignocaine in terminating VT. It may be given orally or intravenously. The oral dose is up to 50 mg.kg1.day1 in divided doses and the intravenous dose is 100 mg slowly up to a maximum of 1 g. This may be followed by an infusion of 26 mg.min1, which should subsequently be converted to oral therapy.

Mechanism of Action

Procainamide is a class Ia anti-arrhythmic and as such reduces the rate of rise of phase 0 of the action potential by blocking Na+ channels. In addition, it raises the threshold potential and prolongs the refractory period without altering the duration of the action potential. It also antagonises vagal tone but to a lesser extent than quinidine.

Side-Effects

These have limited its use.

• Cardiacfollowing intravenous administration it may produce hypotension, vasodilatation and a reduced cardiac output. It may also precipitate heart block. When used to treat SVT the ventricular response rate may increase. It may also prolong the QT interval and precipitate torsades de pointes.

• Non-cardiacchronically a drug-induced lupus erythematosus syndrome with a positive anti-nuclear factor develops in 2030% of patients (many of whom will be slow acetylators). Other minor effects include gastrointestinal upset, fever and rash. It reduces the antimicrobial effect of sulphonamides by the production of para-aminobenzoic acid.

Kinetics

Procainamide is well absorbed from the gut and has an oral bioavailability of 75%. Its short half-life of 3 hours necessitates frequent administration or slow release formulations. It is metabolized in the liver by amidases and by acetylation to the active N-acetyl procainamide. The latter pathway demonstrates genetic polymorphism so that patients may be grouped as slow or fast acetylators. The slow acetylators are more likely to develop side-effects.

Disopyramide

Disopyramide is a class Ia anti-arrhythmic.

Presentation

It is available as tablets (including slow release) and as a solution containing 10 mg.ml1. The daily oral dose is up to 800 mg in divided doses; the intravenous dose is 2 mg.kg1 over 30 minutes up to 150 mg which is followed by an infusion of

1 mg.kg1.h1 up to 800 mg.day1.

Uses

Disopyramide is used as a second-line agent in the treatment of both SVT and ventricular tachyarrhythmias. When used to treat atrial fibrillation or atrial flutter the ventricular rate should first be controlled with b-blockers or verapamil.

Mechanism of Action

Disopyramide is a class Ia anti-arrhythmic and as such reduces the rate of rise of phase 0 of the action potential by blocking Na+ channels. In addition, it raises the

threshold potential and prolongs the refractory period, thereby increasing the duration of the action potential. It also has anticholinergic effects.

Side-Effects

• Cardiacas plasma concentrations rise the QT interval is prolonged (occasionally precipitating torsades de pointes), myocardial contractility becomes depressed while ventricular excitability is increased and may predispose to re-entry arrhythmias. Cardiac failure and cardiogenic shock occur rarely.

• Non-cardiacanticholinergic effects (blurred vision, dry mouth and occasionally urinary retention) often prove unacceptable.

Kinetics

Disopyramide is well absorbed from the gut and has an oral bioavailability of 75%. It is only partially metabolized in the kidney, the majority of the drug being excreted in the urine unchanged. Its elimination half-life is about 5 hours but this increases significantly in patients with renal or cardiac failure.

Propafenone

Propafenone is similar in many respects to flecainide.

Presentation

It is available only as film coated tablets in the UK although it has been used intravenously at a dose of 12 mg.kg1. The oral dose is initially 600900 mg followed by 150300 mg bd or tds.

Uses

Propafenone is used as second line therapy for resistant SVT, including atrial fibrillation and flutter, and also for ventricular tachyarrhythmias.

Mechanism of Action

Propafenone prevents the fast Na+ flux into cardiac tissue and prolongs phase 0 of the action potential. The duration of the action potential and refractory period is prolonged especially in the conducting tissue. The threshold potential is increased and cardiac excitability reduced by an increase in the ventricular fibrillation threshold. At higher doses it may exhibit some b-blocking properties.

Side-Effects

Propafenone is generally well tolerated.

• Cardiacowing to its weak b-blocking actions it should be used with caution in those with heart failure.

• Non-cardiacit may produce minor nervous system effects and at higher doses gastrointestinal side-effects may become more prominent. It may worsen myasthenia gravis. Propafenone increases the plasma levels of concurrently administered digoxin and warfarin. It may precipitate asthma due to its b-blocking properties.

Kinetics

Absorption from the gut is nearly complete and initially oral bioavailability is 50%. However, this increases disproportionately to nearly 100% as the enzymes involved in first-pass metabolism become saturated. It is more than 95% protein-bound. Hepatic metabolism ensures that only tiny amounts are excreted unchanged. However, the enzyme responsible for its metabolism demonstrates genetic polymorphism so that affected patients may have an increased response.

Sotalol

Sotalol is a b-blocker but also has class I and III anti-arrhythmic activity.

Presentation

It is available as tablets and as a solution containing 40 mg in 4 ml. It is a racemic mixture, the D-isomer conferring the class III activity while the L-isomer has both class III and b-blocking actions.

Uses

Sotalol is used to treat ventricular tachyarrhythmias and in the prophylaxis of paroxysmal SVT. The oral dose is 80160 mg bd and the intravenous dose is 50100 mg over 20 minutes.

Mechanism of Action

Sotalol prolongs the duration of the action potential so that the effective refractory period is prolonged in the conducting tissue. It is also a non-selective b-blocker and is more effective at maintaining sinus rhythm following DC cardioversion for atrial fibrillation than other b-blockers. The ventricular rate is also well controlled if the rhythm degenerates back into atrial fibrillation.

Side-Effects

• Cardiacthe most serious side-effect is precipitation of torsades de pointes which occurs in less than 2% of those being treated for sustained VT or VF. It is more common with higher doses, a prolonged QT interval and electrolyte imbalance. It may precipitate heart failure.

• Non-cardiacbronchospasm, masking of symptoms of hypoglycaemia, visual disturbances and sexual dysfunction are all rare.

Kinetics

Sotalol is completely absorbed from the gut and its oral bioavailability is greater than 90%. It is not plasma protein-bound and is not metabolized. Approximately 90% is excreted unchanged in the urine while the remainder is excreted in bile. Renal impairment significantly reduces clearance.

Digoxin Toxicity

Phenytoin

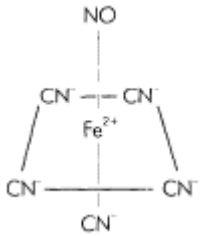
While phenytoin is mainly used for its antiepileptic activity it has a limited role in the treatment of arrhythmias associated with digoxin toxicity.

It depresses normal pacemaker activity while augmenting conduction through the conducting system especially when this has become depressed by digoxin. It also demonstrates class I anti-arrhythmic properties by blocking Na+ channels.

15
Vasodilators

- Sodium nitroprusside
- Nitrates
- Potassium channel activators
- Calcium channel antagonists
- Miscellaneous

Sodium Nitroprusside (SNP)



SNP is an inorganic complex and functions as a prodrug.

Presentation

It is presented in vials as a lyophilized reddish brown powder containing 50 mg SNP. When reconstituted in 5% dextrose it produces a light orange or strawcoloured solution with pH 4.5. If exposed to sunlight it will turn darker brown or blue due to liberation of cyanide (CN) ions at which point the solution should be discarded. Infusions may be protected from sunlight by aluminium foil or opaque syringes and giving sets.

Uses

SNP is usually administered as a 0.0050.020% (50200 µg.ml1) intravenous infusion, the dose of 0.56 µg.kg1 min1 being titrated to effect. The onset of action is within 3 minutes and due to its rapid breakdown its effects are short lived. Various

dose regimes are recommended and are all designed to avoid CN toxicity and thiocyanate (SCN) levels exceeding 100 µg.ml1. Up to 4 µg.kg1.min1 may be used chronically while no more than 1.5 µg.kg1.min1 is recommended during anaesthesia. It is not available orally.

Mechanism of Action

SNP vasodilates arteries and veins by the production of nitric oxide (NO). This activates the enzyme guanylate cyclase leading to increased levels of intracellular cyclic GMP. While Ca2+ influx into vascular smooth muscle in inhibited, its uptake into smooth endoplasmic reticulum is enhanced so that cytoplasmic levels fall, resulting in vasodilation.

Effects

• Cardiovasculararterial vasodilation reduces the systemic vascular resistance and leads to a drop in blood pressure. Venous vasodilation increases the venous capacitance and reduces preload. Cardiac output is maintained by a reflex tachycardia. However, for those patients with heart failure the reduction in pre- and afterload will increase cardiac output with no increase in heart rate. The ventricular wall tension is reduced and myocardial oxygen consumption is reduced. It has no direct effects on contractility. Some patients develop tachyphylaxis, the exact mechanism of which is unclear.

• RespiratorySNP may inhibit pulmonary hypoxic vasoconstriction and lead to increased shunt. Supplemental oxygen may help.

• Central nervous systemintracranial pressure is increased due to cerebral vasodilation and increased cerebral blood flow. However, cerebral autoregulation is maintained well below the normal limits during SNP infusion. In addition, cerebral function monitoring shows depressed cerebral function at a higher blood pressure when hypotension is induced by trimetaphan compared with SNP.

• Endocrineplasma catecholamine and renin levels rise during SNP infusion.

• Gutparalytic ileus has been reported following hypotensive anaesthesia induced by SNP. It is not clear if this is a direct effect or due to reduced mesenteric blood flow or simply due to opioids.

• Generalthe following effects are reversed when the rate of infusion is slowed: nausea and vomiting, dizziness, abdominal pain, muscle twitching and retrosternal pain.

Kinetics

SNP is not absorbed following oral administration. It has a short half-life and its duration of action is less than 10 minutes. However, the half-life of SCN is 2 days.

Metabolism

The metabolism of SNP is complicated (Figure 15.1). Initially within the red blood cell it reacts with oxyhaemoglobin to form NO, five CN ions and methaemoglobin. The methaemoglobin may then combine with CN to form cyanomethaemoglobin, which is thought to be non-toxic.

The remaining CN is then able to escape from the red blood cell where it is converted in the liver and kidney by the mitochondrial enzyme rhodanase with the addition of a sulphydryl group to form thiocyanate (SCN). Red blood cells contain the enzyme thiocyanate oxidase, which can convert SCN back to CN, but most SCN is excreted in the urine. SCN has an elimination half-life of 2 days but

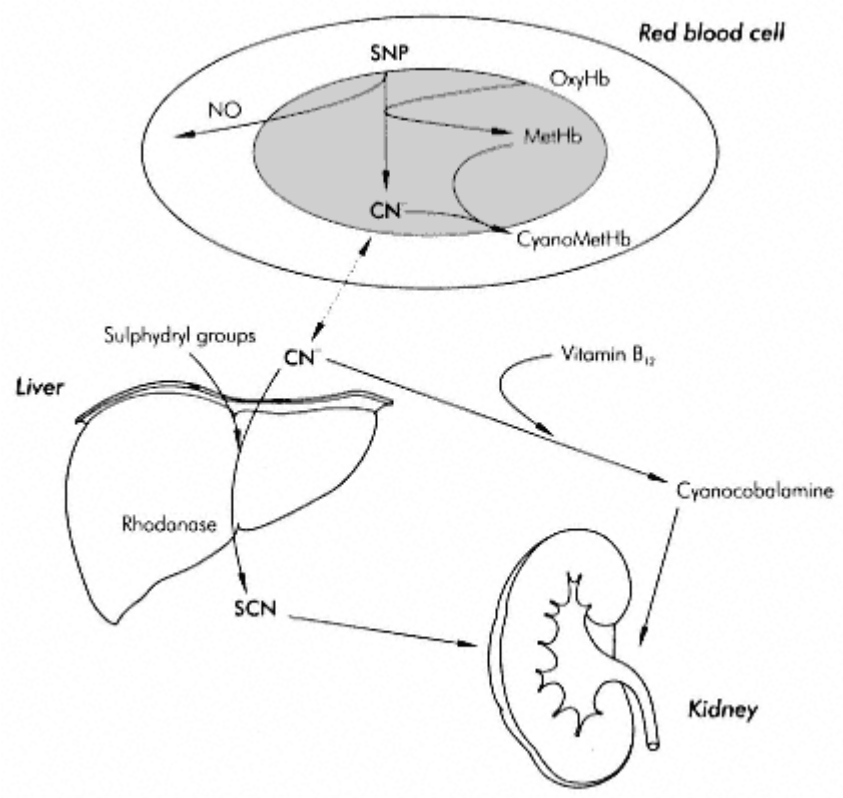


Figure 15.1:
Metabolism of sodium nitroprusside (SNP). CN, cyanide; SCN, thiocyanate.

this may increase to 7 days in the presence of renal impairment. Alternatively CN combines with hydroxycobalamin (vitamin B12) to form cyanocobalamin, which forms a non-toxic store of CN and can be excreted in the urine.

Toxicity

The major risk of toxicity comes from CN, although SCN is also toxic.

Free CN can bind cytochrome oxidase and impair aerobic metabolism. In doing so a metabolic acidosis develops and the mixed venous oxygen saturation increases as tissues become unable to utilize oxygen. Other signs include tachycardia, arrhythmias, hyperventilation and sweating. Plasma CN levels above 8 µg.ml1 result in toxicity. It should be suspected in those who are resistant to SNP despite an adequate dose and in those who develop tachyphylaxis. It is more likely to occur in patients with hypothermia, severe renal or hepatic failure and those with vitamin B12 deficiency.

The management of CN toxicity involves halting the SNP infusion and optimizing oxygen delivery to tissues. Three treatments are useful:

- Dicobalt edetate, which chelates CN ions.

- Sodium thiosulphate, which provides additional sulphydryl groups to facilitate the conversion of CN to SCN. This is sometime used as prophylaxis.

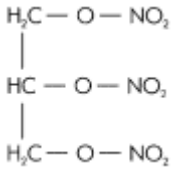
- Nitriteseither sodium nitrite or amyl nitrite will convert oxyhaemoglobin to methaemoglobin, which has a higher affinity for CN than cytochrome oxidase.

While vitamin B12 is required to complex CN to cyanocobalamin it is of little value in the acute setting. It is however sometimes used as prophylaxis.

SCN is 100 times less toxic than CN but its toxic effects may become significant if it is allowed to accumulate during prolonged administration especially in those with impaired renal function. Its accumulation is also more likely in those being given prophylactic sodium thiosulphate as it promotes the production of SCN.

Nitrates

Glyceryl Trinitrate (GTN)



GTN is an organic nitrate

Presentation

GTN is prepared in the following formulations: an aerosol spray delivering 400 µg per metered dose and tablets containing 300600 µg, both used as required sublingually. Modified release tablets containing 15 mg for buccal administration are placed between the upper lip and gum and are used at a maximum dose of 5 mg tds while the 2.610 mg modified-release tablets are to be swallowed and used at a maximum dose of 12.8 mg tds. The transdermal patch preparation releases 515 mg/24 hours, and should be resited at a different location on the chest. The clear colourless solution for injection contains 15 mg.ml1 and should be diluted to a 0.01% (100 µg.ml1) solution before administration by an infusion pump and is used at 10200 µg.min1. GTN is absorbed by polyvinyl chloride; therefore, special polyethylene administration sets are preferred. GTN will explode if heated so transdermal preparations should be removed before DC cardioversion.

Uses

GTN is used in the treatment and prophylaxis of angina, in left ventricular failure associated with myocardial infarction, and following cardiac surgery. It has also been used in the control of intra-operative blood pressure and for oesophageal spasm.

Mechanism of Action

GTN vasodilates veins by the production of nitric oxide. This activates the enzyme guanylate cyclase leading to increased levels of intracellular cyclic GMP. While Ca2+ influx into vascular smooth muscle is inhibited, its uptake into smooth endoplasmic reticulum is enhanced so that cytoplasmic levels fall resulting in vasodilation (Figure 15.4).

Effects

• Cardiovascularin contrast to SNP and despite a similar mechanism of action GTN produces vasodilation predominantly in the capacitance vessels, i.e. veins, although arteries are dilated to some extent.

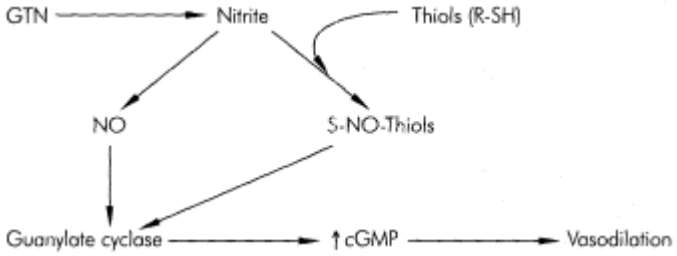


Figure 15.4:
Metabolism of GTN.

Consequently it produces a reduction in preload, venous return, ventricular end-diastolic pressure and wall tension. This in turn leads to a reduction in oxygen demand and increased coronary blood flow to subendocardial regions and is the underlying reason for its use in cardiac failure and ischaemic heart disease. The reduction in preload may lead to a reduction in cardiac output although patients with cardiac failure may see a rise in cardiac output. Postural hypotension may occur. At higher doses systemic vascular resistance falls and augments the fall in blood pressure which, while reducing myocardial work will reduce coronary artery perfusion pressure and time (secondary to tachycardia). Coronary artery flow may be increased directly by coronary vasodilation. Tolerance develops within 48 hours and may be due to depletion of sulphydryl groups within vascular smooth muscle. A daily drug-free period of a few hours prevents tolerance. It has been suggested that infusion of acetylcysteine (providing sulphydryl groups) may prevent tolerance.

- Central nervous systeman increase in intracranial pressure and headache resulting from cerebral vasodilation may occur but is often only problematic at the start of treatment.

- Gutit relaxes the gastrointestinal sphincters including the sphincter of Oddi.

- Haematologicalrarely methaemoglobinaemia is precipitated.

Kinetics

GTN is rapidly absorbed from sublingual mucosa and the gastrointestinal tract although the latter is subject to extensive first-pass hepatic metabolism resulting in an oral bioavailability of less than 5%. Sublingual effects are seen within 3 minutes and last for 3060 minutes.

Hepatic nitrate reductase is responsible for the metabolism of GTN to glycerol dinitrate and nitrite (NO_2) in a process that requires tissue thiols (R-SH). Nitrite is then converted to nitric oxide (NO), which confers its mechanism of action (see above). Under certain conditions nitrite may convert oxyhaemoglobin to methaemoglobin by oxidation of the ferrous ion (Fe^{2+}) to the ferric ion (Fe^{3+}).

Isosorbide Dinitrate (ISDN) and Isosorbide Mononitrate (ISMN)

ISDN is prepared with lactose and mannitol to reduce the risk of explosion. It is well absorbed from the gut and is subject to extensive first-pass metabolism in the liver to isosorbide 2-mononitrate and isosorbide 5-mononitrate (ISMN), both of which probably confer the majority of the activity of ISDN. ISMN has a much

longer half-life (4.5 hours) and is used in its own right. It is not subject to hepatic first-pass metabolism and has an oral bioavailability of 100%. Both are used in the prophylaxis of angina.

Potassium Channel Activators

Nicorandil

Nicorandil (nicotinamidoethyl nitrate) is a potassium-channel activator with a nitrate moiety and as such differs from other potassium-channel activators. It has been used in Japan since 1984 and was launched in the UK in 1994.

Presentation and Uses

Nicorandil is available as tablets and the usual dose is 1030 mg bd. It is used for the treatment and prophylaxis of angina and in the treatment of congestive heart failure and hypertension. It has been used experimentally via the intravenous route.

Mechanism of Action

ATP-sensitive K+ channels are closed during the normal cardiac cycle but are open (activated) during periods of ischaemia when intracellular levels of ATP fall. In the open state K+ passes down its concentration gradient out of the cell resulting in hyperpolarization, which closes Ca2+ channels, resulting in less Ca2+ for myocardial contraction.

Nicorandil activates the ATP-sensitive K+ channels within the heart and arterioles. In addition, nicorandil relaxes venous capacitance smooth muscle by stimulating guanylate cyclase via its nitrate moiety, leading to increased intracellular cGMP.

Effects

• Cardiovascularnicorandil causes venodilation and arterial vasodilation resulting in a reduced pre- and afterload. The blood pressure falls. Left ventricular end-diastolic pressure falls and there is an improved normal and collateral coronary artery blood flow, partly induced by coronary artery vasodilation without a 'steal' phenomenon. An increase in cardiac output is seen in patients with ischaemic heart disease and cardiac failure. It is effective at suppressing torsades de pointes associated with a prolonged QT interval. High concentrations in vitro result in a shortened action potential by accelerated repolarization. It also reduces the size of experimentally induced ischaemia, the mechanism of which is uncertain, so that an alternative, as yet undefined, cardioprotective mechanism has been postulated. Unlike nitrate therapy it is not associated with tolerance during prolonged administration. Contractility and atrio-ventricular conduction is not affected.

- Central nervous systemheadaches, these usually clear with continued therapy.
- Metabolicunlike other antihypertensives it has no effect on lipid profile or glucose control.
- Haematologicalnicorandil inhibits in vitro ADP-induced platelet aggregation (in a similar manner to nitrates), which is associated with an increase of intraplatelet cGMP.
- Miscellaneousgiant oral apthous ulcers have been reported with its use.

Kinetics

Nicorandil is well absorbed from the gut with insignificant first-pass metabolism. The main metabolic route is denitration with 20% excreted as metabolites in the urine. The elimination half-life is 1 hour, although its actions last up to 12 hours, but neither is increased in the presence of renal impairment. It is not plasma protein-bound to any significant extent.

Calcium Channel Antagonists

Despite their disparate chemical structures the Ca2+ channel antagonists are all effective in specifically blocking the entry of Ca2+ through L-type channels while leaving T-, N- and P-type Ca2+ channels unaffected. However, their variable affinity for L-type channels in myocardium, nodal and vascular smooth muscle results in variable effects. They are all useful in the treatment of essential hypertension, although some are also particularly useful in the treatment of angina or arrhythmias.

Verapamil

Verapamil is a racemic mixture and a synthetic derivative of papaverine.

Presentation and Uses

Verapamil is available as 20240 mg tablets, some prepared as modified release and as an oral suspension containing 40 mg/5 ml. The colourless intravenous preparation contains 2.5 mg.ml1. It is used for certain supraventricular arrhythmias (not in atrial fibrillation complicating WolffParkinsonWhite (WPW) syndrome) and

Table 15.1: Chemical classification of Ca2+ channel antagonists.

Class I	phenylalkylamines	verapamil
Class II	dihydropyridines	nifedipine, amlodipine, nimodipine
Class III	benzothiazepines	diltiazem

angina. It has been used to treat hypertension although its negative inotropic properties limit its usefulness in this setting.

Mechanism of Action

The L-isomer has specific Ca2+ channel blocking actions with a particular affinity for those at the sino-atrial (SA) and atrio-ventricular (AV) node, while the D-isomer acts on fast Na+ channels resulting in some local anaesthetic activity.

Effects

• Cardiovascularverapamil acts specifically to slow the conduction of the action potential at the SA and AV node resulting in a reduced heart rate. To a lesser extent it produces some negative inotropic effects and vasodilates peripheral vascular smooth muscle. It is a mild coronary artery vasodilator. Blood pressure falls. It may lead to various degrees of heart block or cardiac failure in those with impaired ventricular function and ventricular fibrillation in those with WPW syndrome.

• Central nervous systemit vasodilates the cerebral circulation.

• Miscellaneousfollowing chronic administration it may potentiate the effects of non-depolarizing and depolarizing muscle relaxants.

Kinetics

Verapamil is well absorbed from the gut but an extensive first-pass hepatic metabolism reduces the oral bioavailability to 20%. Demethylation produces norverapamil, which retains significant anti-arrhythmic properties. It is 90% plasma protein-bound and is mainly excreted in the urine following metabolism, although up to 20% is excreted in bile.

Nifedipine

Presentation and Uses

Nifedipine is available as capsules containing 510 mg, the contents of which may be administered sublingually, and tablets containing 1060 mg, some of which are available as sustained release. The onset of action is 1520 minutes following oral and 510 minutes following sublingual administration. Swallowing the contents of an opened capsule may further reduce the onset time. It is used in the prophylaxis and treatment of angina, hypertension and in Raynaud's syndrome.

Effects

• Cardiovascularnifedipine reduces tone in peripheral and coronary arteries, resulting in a reduced systemic vascular resistance, fall in blood pressure, increased coronary artery blood flow and reflex increases in heart rate and contractility. The cardiac output is increased.

Occasionally these reflex changes worsen the oxygen supply/demand ratio.

Kinetics

Nifedipine is well absorbed following oral administration although hepatic first-pass metabolism reduces its oral bioavailability to 60%. It is 95% plasma protein-bound and has an elimination half-life of 5 hours following oral administration. It is predominantly excreted as inactive metabolites in the urine (Table 15.2).

Nimodipine

Nimodipine is a more lipid-soluble analogue of nifedipine and as such can penetrate the bloodbrain barrier. It is used in the prevention and treatment of cerebral vasospasm following subarachnoid haemorrhage and in migraine. It may be administered orally or intravenously.

Its action may be dependent on blocking a Ca2+ dependent cascade of cellular processes that would otherwise lead to cell damage and destruction.

Diltiazem

Presentation and Uses

Diltiazem is available as 60200 mg tablets, some of which are available as slow release. It is also available in combination with hydrochlorothiazide. It is used for the prophylaxis and treatment of angina and in hypertension.

Table 15.2: Various pharmacological properties of some Ca2+ channel antagonists.

	Absorbed (%)	Oral bioavailability (%)	Protein binding (%)	Active metabolites	Clearance	Elimination half-life (h)
Verapamil	95	20	90	yes	renal	612
Nifedipine	95	60	95	no	renal	25
Diltiazem	95	50	75	yes	60% hepatic, 40% renal	36

Table 15.3: Main cardiovascular effects of some Ca2+ channel antagonists.

	Blood pressure	Heart rate	AV conduction time	Myocardial contractility	Peripheral and coronary artery vasodilation
Verapamil	¯	¯		¯	
Nifedipine	¯	®	®	®	
Diltiazem	¯	¯		¯	

Effects

• Cardiovasculardiltiazem has actions both within the heart and in the peripheral circulation. It prolongs AV conduction time and reduces contractility but to a lesser extent than verapamil. It also reduces the systemic vascular resistance and the blood pressure falls although a reflex tachycardia is not usually seen. Coronary blood flow is increased due to coronary artery vasodilation.

Kinetics

Diltiazem is almost completely absorbed from the gut but hepatic first-pass metabolism reduces the oral bioavailability to 50%. Hepatic metabolism produces an active metabolite, desacetyldiltiazem, which is excreted in the urine. The urine also eliminates 40% of diltiazem in the unchanged form. Approximately 75% is plasma protein-bound.

Miscellaneous

Hydralazine

Presentation and Uses

Hydralazine is available as 2550 mg tablets and as a powder containing 20 mg for reconstitution in water before intravenous administration (5% dextrose should be avoided as it promotes its rapid breakdown). Hydralazine is used orally in the control of chronic hypertension and severe chronic heart failure in conjunction with other agents. It is used intravenously in acute hypertension associated with preeclampsia at 1020 mg. This may take up to 20 minutes to work and repeat doses may be required.

Mechanism of Action

The exact mechanism of action is uncertain but involves the activation of guanylate cyclase and an increase in intracellular cGMP. This leads to a decrease in available intracellular Ca2+ and vasodilation.

Effects

• Cardiovascularits main effect is to reduce arteriolar tone and systemic vascular resistance while the capacitance vessels are less affected. As a result postural hypotension is not usually a problem. Reflex tachycardia and an increase in cardiac output ensue but may be effectively antagonized by b blockade.

• Central nervous systemcerebral artery blood flow increases as a result of cerebral artery vasodilation.

• Renaldespite an increase in renal blood flow, fluid retention, oedema and a reduction in urine output is often seen. This may be overcome by concurrent administration of a diuretic.

• Gutnausea and vomiting are common.

• Miscellaneousperipheral neuropathy and blood dyscrasias. A lupus erythematosus type syndrome is occasionally seen after long-term use and may be more common in slow acetylators and women. It may require long-term corticosteroid therapy.

Kinetics

Hydralazine is well absorbed from the gut but is subject to a variable first-pass metabolism resulting in an oral bioavailability of 2555% depending on the acetylator status of the individual. The plasma half-life is normally 23 hours but this may be shortened to 45 minutes in rapid acetylators. It is 90% protein-bound in the plasma. Up to 85% is excreted in the urine as acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid. It crosses the placenta and may cause a foetal tachycardia.

Minoxidil

Presentation and Uses

Minoxidil is prepared as 2.510 mg tablets, a 2% solution for intravenous use and a 5% lotion. It is used for severe hypertension and alopecia areata.

Its mechanism of action and principal effects are essentially the same as those of hydralazine. The mechanism by which it stimulates the hair follicle is poorly understood. It may also precipitate hypertrichosis of the face and arms and breast tenderness. It does not cause a lupus erythematosus type reaction.

Kinetics

Minoxidil is well absorbed from the gut and has an oral bioavailability of 90%. It is not protein-bound in the plasma. Its plasma half-life is only 3 hours but its hypotensive effects may last for as long as 3 days. It undergoes hepatic glucuronide conjugation and is subsequently excreted in the urine.

Diazoxide

This vasodilator is chemically related to the thiazide diuretics.

Presentation and Uses

Diazoxide is available as 50 mg tablets and as a solution for intravenous injection containing 15 mg.ml1. It is used intravenously to treat hypertensive emergencies associated with renal disease at 13 mg.kg1 up to a maximum dose of 150 mg,

which may be repeated after 15 minutes. It has also been used to treat intractable hypoglycaemia and malignant islet-cell tumours.

Mechanism of Action

Its hypotensive effects are mediated through altered levels of cAMP in arterioles, producing vasodilation. It may also be due to a reduced Ca2+ influx. Its biochemical effects are due to inhibition of insulin secretion and increased release of catecholamines.

Effects

• Cardiovasculardiazoxide produces arteriolar vasodilation with little effect on capacitance vessels. As a result the blood pressure falls and there is an increase in heart rate and cardiac output. Postural hypotension is not a problem.

• Metabolicit increases the levels of glucose, catecholamines, renin and aldosterone. It also causes fluid retention (despite its chemical relation to the thiazides) which may require treatment with a loop diuretic.

• Miscellaneousthe following effects may occur: nausea, especially at the start of treatment, extra-pyramidal effects including occulogyric crisis, thrombocytopenia and hyperuricaemia.

Kinetics

Diazoxide is well absorbed from the gut with an oral bioavailability of 80%, and is extensively protein-bound in the plasma (about 90%). The hyperglycaemic effects last about 8 hours while the hypotensive effects last about 5 hours. The plasma half-life, however, may last up to 36 hours. It is partly metabolized in the liver, being excreted in the urine as unchanged drug and as inactive metabolites.

16
Antihypertensives

- Drugs affecting the reninangiotensinaldosterone system
- Adrenergic neurone blockade
- Centrally acting
- Ganglion blockade
- Diuretics
- Adrenoreceptor antagonists
- Ca2+ channel antagonists

ReninAngiotensinAldosterone System

Physiology

The juxtaglomerular apparatus within the kidney consists of three distinct cell types:

- Juxtaglomerular cells form part of the afferent arteriole as it enters the glomerulus and are supplied by sympathetic nerves. They contain prorenin, which is converted to the acid protease renin before systemic release.
- The macula densa is a region of cells at the start of the distal convoluted tubule which lie adjacent to the juxtaglomerular cells of the same nephron.
- Agranular lacis cells, which lie between the afferent and efferent arterioles adjacent to the glomerulus.

Under the following conditions the juxtaglomerular apparatus will cause the release of renin into the circulation:

- reduced renal perfusion

- reduced Na+ at the macula densa
- stimulation of the renal sympathetic fibres via b1 adrenoreceptors

Renin (half-life 80 min) splits the decapeptide angiotensin I from the circulating plasma protein angiotensinogen, which is synthesized in the liver and is present in the a2-globulin fraction of plasma proteins. Angiotensin-converting enzyme (ACE) converts angiotensin I to the active octapeptide angiotensin II, and also inactivates bradykinin. Angiotensin II is broken down in the kidney and liver to inactive metabolites and angiotensin III, which retains some activity (Figure 16.1).

Angiotensin II

Mechanism of Action

Two subtypes of angiotensin receptor exist, AT1 and AT2. Angiotensin has a greater affinity for AT1 receptors which are G protein-coupled.

Effects

- Potent vasoconstriction (about five times as potent as noradrenaline). Directly on arterioles and indirectly via central mechanisms.

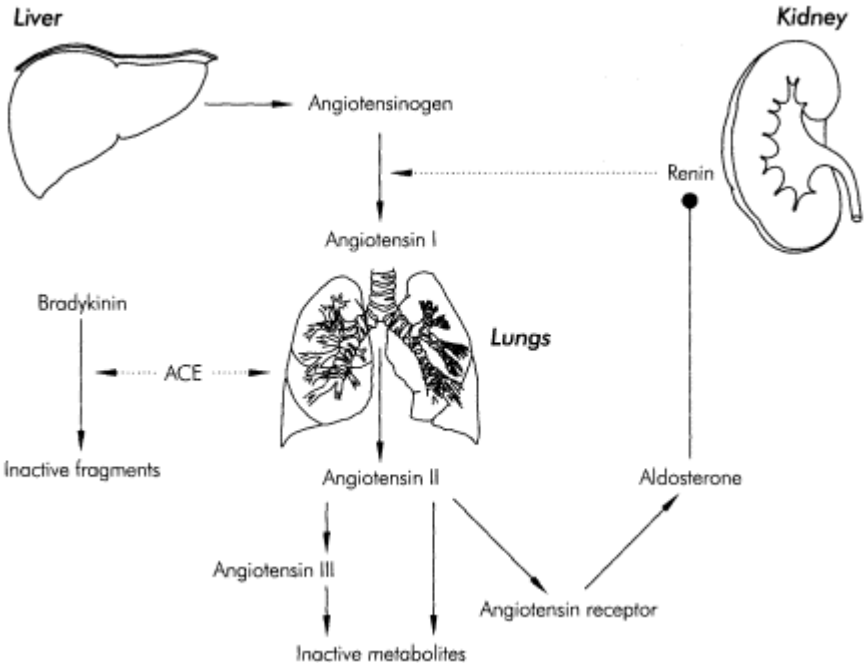


Figure 16.1:
Reninangiotensinaldosterone system. - - - - ►, Enzyme action; —● negative feedback.

• Blockade of noradrenaline re-uptake (uptake 1) at sympathetic nerves and sympathetic nervous system activation.

• Central effectsit increases thirst and the release of antidiuretic hormone (ADH) and adrenocorticotrophic hormone (ACTH).

• It stimulates the release of aldosterone from the adrenal cortex, and inhibits the release of renin from the juxtaglomerular cells.

• Reduced glomerular filtration rate.

The ACE inhibitors and more recently the angiotensin II receptor antagonists are now widely used in the treatment of hypertension. b-Blockers (cf. chapter 13) reduce sympathetically mediated release of renin, which contributes to their antihypertensive effects.

Angiotensin-Converting Enzyme (ACE) Inhibitors:
Captopril

Presentation and Uses

Captopril is available as 12.550 mg tablets that may also be combined with hydrochlorothiazide. It is used in the treatment of hypertension especially in insulin-dependent diabetics with nephropathy. It is useful in all grades of heart failure and improves the prognosis in myocardial infarction with left ventricular dysfunction. The initial dose is 12.5 mg although 6.25 mg may be prudent in heart failure.

Mechanism of Action

Captopril is a competitive ACE inhibitor and therefore prevents the formation of angiotensin II and its effects. Afterload is reduced to a greater degree than preload.

Effects

• Cardiovascularcaptopril reduces the systemic vascular resistance significantly, resulting in a fall in blood pressure. The fall in afterload may increase the cardiac output particularly in those with heart failure. Heart rate is usually unaffected but may increase. Baroreceptor reflexes are also unaffected. Transient hypotension may occur at the start of treatment, which should therefore be initiated in hospital for patients with anything more than mild heart failure.

• Respiratorya persistent dry cough may be the result of increased levels of bradykinin, which are normally broken down by ACE.

• Renalrenal blood flow is increased and a natriuresis may ensue. However, where there is bilateral renal artery stenosis or unilateral renal

artery stenosis to a single functioning kidney captopril will reduce glomerular filtration and this may lead to renal failure.

• Metabolicreduced aldosterone release impairs the negative feedback to renin production so that renin levels become elevated. It may also lead to hyperkalaemia and raised urea and creatinine, especially in those with even mildly impaired renal function.

• Miscellaneousrare but serious effects may complicate its use and include angio-oedema, agranulocytosis and thrombocytopenia. Less serious side-effects are more common and include loss of taste, rash, pruritus, fever and apthous ulceration. These are more common with higher doses and in patients with impaired renal function.

• Interactionscaptopril reduces aldosterone release which may result in hyperkalaemia, so it should not be used with potassium-sparing diuretics. It has been associated with unexplained hypoglycaemia in insulin-and non-insulin-dependent diabetics. These effects usually decrease with continued treatment. Non-steroidal anti-inflammatory drugs reduce captopril's antihypertensive effects and may precipitate renal failure.

Kinetics

Captopril is well absorbed from the gut and has an oral bioavailability of 65%. It is 25% plasma protein-bound. Approximately 50% is oxidized in the liver to the dimer and mixed sulphides all of which are eventually excreted in the urine. It has an elimination half-life of 2 hours, although this will be increased in the presence of renal impairment.

Enalopril

While enalopril shares the common features of the ACE inhibitors it has some differences from captopril:

• enalopril is a prodrug, which is hydrolysed to the active compound enaloprilat

• it has a longer elimination half-life and a longer duration of action (about 24 hours)

Angiotensin II Receptor Antagonists:
Losartan

Losartan is a substituted imidazole compound.

Presentation and Uses

Losartan is available as 2550 mg tablets and in combination with hydrochlorothiazide. It is used in the treatment of hypertension where dry cough proves an unacceptable side-effect of ACE inhibitor therapy.

Mechanism of Action

Losartan is a specific angiotensin II receptor (type AT1) antagonist at all sites within the body. It blocks the negative feedback of angiotensin II on renin secretion, which therefore increases, leading to increased angiotensin II. This has little impact due to comprehensive AT1 receptor blockade.

Effects

These are broadly similar to those of the ACE inhibitors.

• Metabolicas it does not block the actions of ACE, bradykinin may be broken down in the usual manner (by ACE). As a result, bradykinin levels are not raised and the dry cough seen with ACE inhibitors does not complicate its use.

Kinetics

Losartan is well absorbed from the gut but undergoes significant first-pass metabolism to an active carboxylic acid metabolite (which acts in a non-competitive manner), and several other inactive compounds. It has an oral bioavailability of 30%, and is 99% plasma protein-bound. Its elimination half-life is 2 hours while the elimination half-life of the active metabolite is 7 hours. Less than 10% is excreted unchanged in an active form in the urine. The inactive metabolites are excreted in bile and urine.

Adrenergic Neurone Blockade

This group of drugs interferes with the release of noradrenaline from adrenergic neurones.

Physiology

Noradrenaline is synthesized from tyrosine (see Chapter 12) within the adrenergic nerve terminal. It is held in storage vesicles and subsequently released into the neuronal cleft to act on adrenoreceptors. Its actions are terminated by:

• Uptake 1noradrenaline is taken back into the nerve terminal by a high-affinity transport system. This provides the main route for terminating its effects. Within the neurone it is recycled and returned to storage vesicles. However, while in the cytoplasm some may be de-aminated by monoamine oxidase (MAO).

• Uptake 2noradrenaline diffuses away from the nerve terminal into the circulation where it is taken up by extra-neuronal tissues including the liver and metabolized by catechol O-methyltransferase (COMT).

Guanethidine

Presentation and Uses

Guanethidine is available as tablets and as a colourless solution for injection containing 10 mg.ml1. It has been used as an antihypertensive agent but is currently used only for the control of sympathetically mediated chronic pain. The initial antihypertensive dose is 10 mg.day1, which is increased to a maintenance dose of 3050 mg.day1. A dose of 20 mg is used when performing an intravenous regional block for chronic pain. Repeated blocks are usually required.

Mechanism of Action

Guanethidine gains access to the adrenergic neurone by utilizing the uptake 1 transport mechanism. Following intravenous administration there is some initial hypotension by direct vasodilation of arterioles. Subsequently, it displaces noradrenaline from its binding sites, which may cause transient hypertension. Finally, guanethidine reduces the blood pressure by preventing the release of what little noradrenaline is left in the nerve terminal. Oral administration does not produce the same triphasic response, as its onset of action is much slower. It does not alter the secretion of catecholamines by the adrenal medulla.

Effects

• Cardiovascularhypotension is its main action. Postural hypotension is common as it blocks any compensatory rise in sympathetic tone. Fluid retention leading to oedema may occur.

• Gutdiarrhoea is common.

• Miscellaneousfailure to ejaculate.

• Drug interactionsdrugs that block uptake 1 (tricyclic antidepressants, cocaine) prevent guanethidine from entering the nerve terminal and disrupting noradrenaline storage. They therefore antagonize guanethidine.

Up-regulation of adrenoreceptors follows the long-term use of guanethidine so that these patients are very sensitive to direct acting sympathomimetic amines.

Kinetics

Following oral administration guanethidine is variably and incompletely absorbed. Hepatic first-pass metabolism results in an oral bioavailability of 50%. It is not bound by plasma proteins and does not cross the bloodbrain barrier. It has an

elimination half-life of several days. Elimination is by hepatic metabolism and excretion of unchanged drug and its metabolites in the urine.

Reserpine

Reserpine is no longer available in the UK. It is a naturally occurring alkaloid that was widely used to treat hypertension that failed to respond to b-blockers or diuretics.

Mechanism of Action

Reserpine acts centrally and peripherally by preventing storage vesicles incorporating noradrenaline from neuronal cytoplasm leading to rapid de-amination by mitochondrial MAO and noradrenaline depleted neurones. Serotonin is also depleted.

Effects

• Cardiovascularhypotension is mainly a result of a reduced cardiac output and systemic vascular resistance. Postural hypotension is rarely a problem, but nasal congestion is less well tolerated.

• Central nervous systemdepression, lethargy and nightmares are due to reserpine's ability to cross the bloodbrain barrier. Extrapyramidal effects may also be seen. General anaesthetic requirements are decreased.

• Gutdiarrhoea and increased gastric acid secretions may lead to epigastric pain.

• Miscellaneoussexual dysfunction, hyperprolactinaemia, gynaecomastia and galactorrhoea are seen rarely.

• Drug interactionspatients taking reserpine will exhibit increased sensitivity to directly acting sympathomimetic amines (adrenoreceptor upregulation) but reduced sensitivity to indirectly acting sympathomimetic amines (depleted noradrenaline stores).

Kinetics

Following absorption from the gut reserpine is metabolized slowly in the liver. Some metabolic products are excreted in the urine while most appears to be excreted unchanged in the bile. It has a half-life of many days. It crosses the placenta and bloodbrain barrier and also reaches breast milk.

Metirosine

Metirosine is a competitive inhibitor of tyrosine hydroxylase (cf p165) and can therefore prevent the synthesis of catecholamines. It should only be used to manage hypertension associated with phaeochromocytoma.

It may cause severe diarrhoea, sedation, extrapyramidal effects and hypersensitivity reactions.

Centrally Acting

Methyldopa

Presentation and Uses

Methyldopa is available as film-coated tablets containing 125500 mg, and as an oral suspension containing 50 mg.ml1. The rarely used intravenous preparation is colourless and contains 50 mg.ml1 and uses sodium metabisulphite as the preservative. It is used at 250 mg tds increasing to a maximum of 3 g.day1 to control hypertension, especially that associated with pregnancy.

Mechanism of Action

Methyldopa readily crosses the bloodbrain barrier where it is decarboxylated to a-methyl-noradrenaline, which is a potent a2-agonist. It retains limited a1-agonist properties (a2:a1 ratio 10:1). Stimulation of presynaptic a2 receptors in the nucleus tractus solitarii forms a negative feedback loop for further noradrenaline release so that a-methyl-noradrenaline reduces centrally mediated sympathetic tone, leading to a reduction in blood pressure.

Effects

- Cardiovascularits main effect is a reduction in systemic vascular resistance leading to a fall in blood pressure. Postural hypotension is occasionally a problem. Cardiac output is unchanged despite a relative bradycardia. Rebound hypertension may occur if treatment is stopped suddenly but this is less common than with clonidine.

- Central nervous systemsedation is common, while dizziness, depression, nightmares and nausea are less common. The MAC of volatile anaesthetics is reduced.

- Haematologicala positive direct Coombs' test is seen in 1020% of patients taking methyldopa. Thrombocytopenia and leucopenia occur rarely.

- Allergicit may precipitate an auto-immune haemolytic anaemia. Eosinophilia associated with fever sometimes occurs within the first few weeks of therapy. A hypersensitivity reaction may cause myocarditis.

- Renalurine may become darker in colour when exposed to air, due to the breakdown of methyldopa or its metabolites.

- Hepaticliver function may deteriorate during long-term treatment and fatal hepatic necrosis has been reported.

• Miscellaneousit fluoresces at the same wavelengths as catecholamines so that assays of urinary catecholamines may be falsely high. Assays of VMA are not affected. It may cause constipation and gynaecomastia (due to suppressed prolactin release).

Kinetics

Methyldopa is erratically absorbed from the gut and has a very variable oral bioavailability and a slow onset of action. It is subject to hepatic first-pass metabolism, being converted to the O-sulphate. Less than 20% is bound to plasma proteins. Approximately 50% is excreted unchanged in the urine.

Clonidine

Clonidine is an a-agonist with an affinity for a2 receptors 200 times that for a1 receptors. Some studies identify it as a partial agonist.

Presentation and Uses

Clonidine is available as 25300 µg tablets and as a colourless solution for injection containing 150 µg.ml1. A transdermal patch is available but this takes 48 hours to achieve therapeutic levels. It is used in the treatment of hypertension, acute and chronic pain, the suppression of symptoms of opioid withdrawal and to augment sedation during ventilation of the critically ill patient.

Mechanism of Action

The useful effects of clonidine rest on its ability to stimulate a2 receptors in the lateral reticular nucleus resulting in reduced central sympathetic outflow, and in the spinal cord where they augment endogenous opiate release and modulate the descending noradrenergic pathways involved in spinal nociceptive processing. MAC appears to be reduced by stimulation of central postsynaptic a2 receptors.

Transmembrane signalling of a2 receptors is coupled to Gi, leading to reduced intracellular cAMP. K+ channels are also activated.

Effects

• Cardiovascularfollowing intravenous administration the blood pressure may rise due to peripheral a1 stimulation, but this is followed by a more prolonged fall in blood pressure. Cardiac output is well maintained despite a bradycardia. The PR interval is lengthened, atrio-ventricular nodal conduction depressed and the baroreceptor reflexes are sensitized by clonidine resulting in a lower heart rate for a given increase in blood pressure. Its effects on the coronary circulation are complicated as any direct vasoconstriction may be offset by a reduction in sympathetic tone and by the release of local nitric oxide. It stabilizes the cardiovascular responses to peri-operative stimuli. Rebound hypertension

is seen more commonly when a dose of more than 1.2 g.day1 is stopped abruptly. This is due to peripheral vasoconstriction and increased plasma catecholamines and may be exacerbated by b blockade (leaving vasoconstriction unopposed). Increasing doses have a ceiling effect and are limited by increasing a1 stimulation.

• Central nervous systemit produces sedation and a reduction of up to 50% in the MAC of volatile agents. It is anxiolytic at low doses but becomes anxiogenic at higher doses.

• Analgesiaclonidine has been used via the subarachnoid and epidural routes. It provides prolonged analgesia with no respiratory depression and appears to act synergistically with concurrently administered opioids. It does not produce motor or sensory blockade. Clonidine also appears to reduce postoperative opioid requirement when administered intravenously.

• Renal systema number of mechanisms including inhibition of release of ADH have been implicated as the cause of diuresis during its use.

• Respiratoryin contrast to opioids it does not produce significant respiratory depression.

• Endocrinethe stress response to surgical stimulus is inhibited. Insulin release is inhibited although this rarely increases blood sugar levels.

• Haematologicaldespite the presence of a2 adrenoreceptors on platelets, therapeutic doses of clonidine do not promote platelet aggregation and its sympatholytic effects block adrenaline-induced platelet aggregation.

Kinetics

Clonidine is rapidly and almost completely absorbed after oral administration, achieving an oral bioavailability of nearly 100%. It is 20% plasma protein-bound and has a volume of distribution of about 2 l.kg1. The elimination half-life of clonidine is between 9 and 18 hours, with approximately 50% the drug being metabolized in the liver to inactive metabolites, while the rest is excreted unchanged in the urine. The dose should be reduced in the presence of renal impairment.

Dexmedetomidine

Medetomidine is an a2-agonist that has been used widely in veterinary practice for its sedation and analgesic properties.

Presentation and Uses

Medetomidine is a racemic mixture but only the D-stereoisomer is active, so it has been developed as dexmedetomidine.

Mechanism of Action

This is similar to that of clonidine although it is more potent and has a higher affinity for the a2 receptor (a2:a1 ratio 1600:1). It is a full agonist.

Effects

These are broadly similar to those of clonidine.

Kinetics

Oral absorption is unpredictable but does avoid the initial hypertension that parenteral administration produces. It has an elimination half-life of 2 hours.

Atipamezole

Atipamezole is a selective a2 antagonist that crosses the bloodbrain barrier to reverse the sedation and analgesia associated with clonidine and dexmedetomidine. At 2 hours its elimination half-life is similar to dexmedetomidine with obvious clinical benefit.

Ganglion Blockade

This group of drugs competitively antagonizes nicotinic receptors at both parasympathetic and sympathetic ganglia and also at the adrenal cortex. Ganglion blockers do not inhibit nicotinic receptors at the neuromuscular junction although some muscle relaxants (tubocurare) may demonstrate some ganglion blocking properties.

Trimetaphan

Trimetaphan is a quaternary ammonium compound.

Presentation and Uses

Trimetaphan is available as a clear pale yellow solution for intravenous injection containing 50 mg.ml1. It was used previously via the oral route to treat essential hypertension but drugs with better side-effect profiles have superseded it. Its sole current use is to induce hypotensive anaesthesia at 14 mg.min1.

Mechanism of Action

Trimetaphan is a competitive antagonist at all nicotinic ganglionic receptors including those at the adrenal cortex and has a direct vasodilator effect on peripheral vessels. Histamine is also released but may not be significant in producing hypotension.

Effects

• Cardiovascularthe onset of hypotension is rapid when used by intravenous infusion. Pre- and afterload falls and there may be a compensatory increase in heart rate to maintain cardiac output.

• Central nervous systemcerebral blood flow is not reduced as long as the preload is maintained with intravenous fluid and the mean blood pressure remains above approximately 50 mmHg. The cerebral metabolic rate is unchanged and it does not cross the bloodbrain barrier to any extent.

• Respiratoryhistamine release may induce bronchospasm.

• Parasympatheticowing to parasympathetic ganglion blockade the following effects are seen: constipation, urinary retention, dry mouth, mydriasis, increased intra-occular pressure and variable tachycardia. These may complicate recovery from anaesthesia.

• Miscellaneousit inhibits plasma cholinesterase and prolongs the effects of depolarizing and non-depolarizing muscle relaxants, although this is variable.

Kinetics

Data are limited but it is mainly excreted unchanged in the urine. There may be some plasma hydrolysis. It crosses the placenta and has been associated with meconium ileus in neonates.

Hexamethonium (C6)

This quaternary ammonium compound has similar effects to trimetaphan. It is no longer used in the UK.

Diuretics

See Chapter 20.

Adrenoreceptor Antagonists

See Chapter 13.

Ca2+ Channel Antagonists

See Chapter 15.

SECTION 4
OTHER IMPORTANT DRUGS

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17
Central Nervous System

- Hypnotics and anxiolytics
- Antidepressants
- Anticonvulsants

Hypnotics and Anxiolytics

Physiology

g-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter within the central nervous system (CNS) and acts via two different receptor subtypes, GABAA and GABAB:

- GABAAthis receptor is a ligand-gated Cl ion channel. It consists of five subunits (2a, b, d and geach having a number of variants) arranged to form a central ion channel. GABA binds to and activates GABAA receptors and increases the opening frequency of its Cl channel, augmenting Cl conductance and thereby hyperpolarizing the neuronal membrane. Cl ion conductance is potentiated by the binding of benzodiazepines (BDZs) to the a subunit of the activated receptor complex. GABAA receptors are essentially (but not exclusively) postsynaptic and are widely distributed throughout the CNS.

- GABABthis receptor is metabotropic (i.e. acts via a G protein and second messenger), and when stimulated it increases K+ conductance, thereby hyperpolarizing the neuronal membrane. GABAB receptors are located both presynaptically on nerve terminals and postsynaptically in many regions of the brain, as well as in the dorsal horn of the spinal cord. Baclofen acts only via GABAB receptors to reduce spasticity.

BDZs modulate the effects of GABA at GABAA receptors. The specific a-subunit type determines the BDZ pharmacologyanxiolytic or sedative. Two BDZ receptor subtypes have been identified: BZ1, found in the spinal cord and cerebellum

responsible for anxiolysis; and BZ2, found in the spinal cord, hippocampus and cerebral cortexresponsible for sedative and anticonvulsant activity.

Benzodiazepines (BDZs)

Uses

BDZs are used commonly in anaesthesia as premedication and to sedate patients during minor procedures. They are also used more widely as anxiolytics, hypnotics and anticonvulsants.

Midazolam

Presentation

Midazolam is presented as a clear solution at pH 3.5. It is unique among the BDZs in that its structure is dependent on the surrounding pH. At pH 3.5 its ring structure is open resulting in an ionized molecule, which is therefore water-soluble. However, when its surrounding pH is greater than 4 its ring structure closes so that it is no longer ionized and therefore becomes lipid soluble (Figure 17.1). Its pKa is 6.5, so that at physiological pH 89% is present in an unionized form and available to cross lipid membranes.

As it is water-soluble it does not cause pain on injection.

Uses

Midazolam is used intravenously to sedate patients for minor procedures and has powerful amnesic properties. It is also used to sedate ventilated patients in Intensive Care.

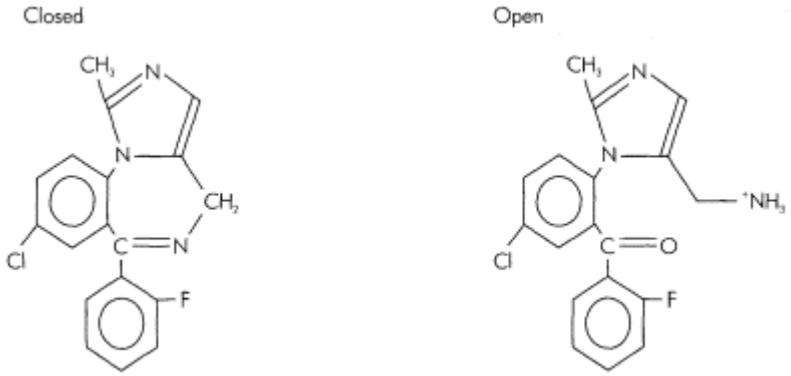


Figure 17.1:
Structures of midazolam.

Kinetics

Midazolam may be given orally (bioavailability approximately 40%), intranasally or intramuscularly as premedication. It has a short duration of action due to distribution. It is metabolized by hydroxylation essentially to inactive compounds that are excreted as glucuronide conjugates in the urine. Less than 5% is metabolized to oxazepam. It is highly protein-bound (approximately 95%) and has an elimination half-life of 14 hours. At 610 ml.kg1.min1 its clearance is larger than that of diazepam and lorazepam so that its effects wear off more rapidly following infusion.

Alfentanil is metabolized by the same hepatic P450 isoenzyme (3A3/4), and when administered together their effects are prolonged.

Diazepam

Diazepam has a high lipid solubility which facilitates its oral absorption and its rapid central effects. It is highly protein-bound (approximately 95%) to albumin and is metabolized in the liver by oxidation to desmethyldiazepam, oxazepam and temazepam all of which are active. It does not induce hepatic enzymes. The glucuronide derivatives are excreted in the urine. It has the lowest clearance of the BDZs discussed here and its half-life is hugely increased by its use as an infusion. (cf. context-sensitive half-time p56).

It may cause some cardiorespiratory depression. Liver failure and cimetidine will prolong its actions by reducing its metabolism. When administered with opioids or alcohol respiratory depression may be more pronounced. In common with other BDZs it reduces the MAC of co-administered anaesthetic agents.

Lorazepam

Lorazepam shares similar pharmacokinetics and actions to other BDZs although its metabolites are inactive. It is used for premedication as an anxiolytic and amnesic. It may also be used in status epilepticus (50100 µg.kg1 i.v., s.1. or p.r. from 1 to 12 years, maximum dose 4 mg; > 12 years, 4 mg).

It is well absorbed following oral or intramuscular administration, highly plasma protein-bound (approximately 95%) and conjugated with glucuronic acid producing inactive metabolites which are excreted in the urine (Figure 17.2).

Table 17.1: Kinetics of some benzodiazepines.

	Diazepam	Midazolam	Lorazepam
Protein binding (%)	95	95	95
Elimination half-life (h)	2045	14	1020
Volume of distribution (l.kg1)	1.01.5	1.01.5	0.751.30
Active metabolites	yes	no	no
Clearance (ml.kg1.min1)	0.20.5	610	1.01.5

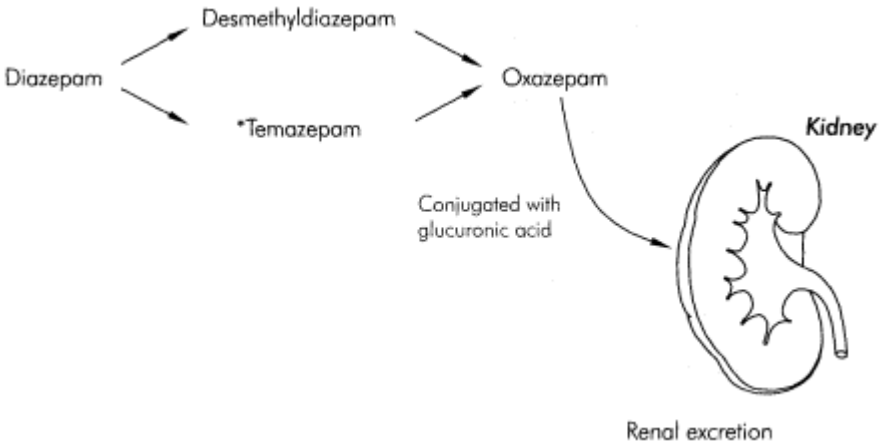


Figure 17.2:

Metabolism of diazepam. *Less than 5% of temazepam is metabolized to oxazepam.

Flumazenil

Flumazenil is an imidazobenzodiazepine

Uses

Flumazenil is used to reverse the effects of BDZs, i.e. excessive sedation following minor procedures or in the treatment of BDZ overdose. It is given by intravenous injection in 100 µg increments and acts within 2 minutes. Its relatively short half-life (about 1 hour) compared with many BDZs, means that further doses or an infusion may be needed.

Mechanism of Action

Flumazenil is a competitive BDZ antagonist. However, it has some agonist activity as well and its ability to precipitate seizures in certain patients may be due to inverse agonist activity (cf p34).

Effects

These include nausea and vomiting. It may also precipitate anxiety, agitation and seizures especially in epileptic patients.

Kinetics

Flumazenil is 50% plasma protein-bound and undergoes significant hepatic metabolism to inactive compounds that are excreted in the urine.

Antidepressants

Four groups of drugs are used to treat depression:

- tricyclics
- selective serotonin re-uptake inhibitors
- monoamine oxidase inhibitors
- atypical agents

TricyclicsTCAs (Amitriptyline, Nortriptyline, Imipramine, Dothiepin)

As its name suggests, this group of drugs was originally based on a tricyclic ring structure, although now many second-generation drugs contain different numbers of rings.

Uses

TCAs are used to treat depressive illness, nocturnal enuresis and as an adjunct in the treatment of chronic pain.

Mechanism of Action

They competitively block neuronal uptake (uptake 1) of noradrenaline and serotonin (5-HT). In doing so they increase the concentration of transmitter in the synapse. However, the antidepressant effects do not occur within the same time frame, taking up to 2 weeks to work. They also block muscarinic, histaminergic and a-adrenoreceptors, and have non-specific sedative effects (Table 17.2).

Effects

- Central nervous systemsedation and occasionally seizures in epileptic patients.

Table 17.2: Effects of various antidepressants.

	Anticholinergic effects	Sedation	Postural hypotension
TCA			
Amitriptyline	+ + + +	+ + + + + +	
Imipramine	+ +	+ +	+ + +
Nortriptyline	+ +	+ +	+
Desipramine	+	+	+
SSRI			
Fluoxetine	+	nil	+

- Anticholinergic effectsdry mouth, constipation, urinary retention and blurred vision.

- Cardiovascularpostural hypotension especially in the elderly.

Kinetics

TCAs are well absorbed from the gut reflecting their high lipid solubility. They are highly plasma protein-bound and have a high volume of distribution. Metabolism, which shows large interpatient variability, occurs in the liver and often produces active metabolites (e.g. imipramine to desipramine and nortriptyline).

TCA Overdose

This is not uncommon in depressed patients. The features of tricyclic overdose include a mixture of:

- Cardiovascular effectssinus tachycardia is common and there is a dose-related prolongation of the QT interval and widening of the QRS complex. Ventricular arrhythmias are more likely when the QRS complex is longer than 0.16 seconds. Right bundle branch block is also seen. The blood pressure may be high or low but in serious overdose hypotension may be refractory to treatment and culminate in pulseless electrical activity.

- Central effectsexcitation, seizures (correlating with a QRS duration of more than 0.1 seconds) and then depression. Mydriasis is a feature, as is hyperthermia.

- Anticholinergic effects.

Treatment

This includes gastric lavage followed by activated charcoal. Supportive care may require supplementation with specific treatment. Seizures may be treated with benzodiazepines or phenytoin and ventricular arrhythmias with phenytoin or lignocaine. Inotropes should be avoided where possible as this may precipitate arrhythmias. Intravascular volume expansion is usually sufficient to correct hypotension. The anticholinergic effects may be reversed by an anticholinesterase but this is not recommended as it may precipitate seizures, bradycardia and heart failure.

Selective Serotonin Re-Uptake InhibitorsSSRIs (Fluoxetine, Paroxetine, Sertraline, Venlafaxine)

As their name suggests, they selectively inhibit the neuronal re-uptake of 5-HT. They are no more effective than standard antidepressants but do not have their

associated side-effect profile. SSRIs are less sedative, have fewer anticholinergic effects and appear less cardiotoxic in overdose although they are associated with gastrointestinal side-effects (nausea and constipation).

Fluoxetine (Prozac) is an effective antidepressant causing minimal sedation. It is a 50:50 mix of two isomers that are equally active. It is well absorbed and metabolized in the liver by cytochrome P450 enzymes. In addition, there are non-saturable enzymes that prevent an unchecked rise in levels. However, the dose should be reduced in renal failure as accumulation may result. Side-effects include nausea and vomiting, headache, insomnia, reduced libido and mania or hypomania in up to 1%.

Venlafaxine appears to block the re-uptake of both noradrenaline and 5-HT (and to a lesser extent dopamine) while having little effect on muscarinic, histaminergic or a-adrenoreceptors.

Monoamine Oxidase InhibitorsMAOIs

This group of drugs is administered orally for the treatment of resistant depression, obsessive compulsive disorders, chronic pain syndromes and migraine.

MAO is present as a variety of isoenzymes within presynaptic neurones and is responsible for the deamination of amine neurotransmitters. They have been classified as types A and B. Following their inhibition there is an increase in the level of amine neurotransmitters which is thought to be the basis of their central activity. MAO-A preferentially deaminates 5-HT and catecholamines, while MAO-B preferentially deaminates tyramine and phenylethamine.

There are now two generations of MAOIs. The original generation inhibit MAO irreversibly and non-selectively (i.e. MAO-A and -B), while the new generation selectively and reversibly inhibit only MAO-A (RIMA). Neither group is used as first line therapy because of the potential for serious side-effects and hepatotoxicity.

Non-selective Irreversible MAOIs (Phenelzine, Isocarboxazid, Tranylcypromine)

Phenelzine and isocarboxazid are hydrazines while tranylcypromine is a non-hydrazine compound. Tranylcypromine is potentially the most dangerous as it possess stimulant activity.

Effects

In addition to controlling depression they also produce sedation, blurred vision, orthostatic hypotension and hypertensive crises following tyramine rich foods (cheese, pickled herring, chicken liver, Bovril and chocolate) and indirectly acting

sympathomimetics. Hepatic enzymes are inhibited and the hydrazine compounds may cause hepatotoxicity. Interaction with pethidine may precipitate cerebral irritability, hyperpyrexia and cardiovascular instability. Interaction with fentanyl has also been reported.

Selective Reversible MAOIsRIMA (Moclobemide)

Moclobemide causes less potentiation of tyramine than the older generation MAOIs and in general patients do not need the same level of dietary restriction. However, some patients are especially sensitive to tyramine and so all patients should be advised to avoid tyramine-rich foods and indirectly acting sympathomimetic amines.

It is completely absorbed from the gut but undergoes significant first-pass metabolism resulting in an oral bioavailability of 6080%. It is metabolized in the liver by cytochrome P450 and up to 2% of the Caucasian and 15% of the Asian population have been shown to be slow metabolizers. The metabolites are excreted in the urine.

MAOIs and General Anaesthesia

Those patients taking MAOIs and presenting for emergency surgery should not be given pethidine or any indirectly acting sympathomimetic amines (e.g. ephedrine). If cardiovascular support is indicated, directly acting agents should be used, but with extreme caution as they also may precipitate exaggerated hypertension. The elective case presents potential difficulties. If MAOI therapy is withdrawn for the required 1421 days before surgery the patient may suffer a relapse of their depression with potentially disastrous consequences. However, the newer agents may control depression more effectively and reduce the chance of a serious peri-operative drug interaction.

Indirectly acting sympathomimetic amines are heavily dependent on MAO for their metabolism and therefore may produce exaggerated hypertension and arrhythmias when administered with MAOI. The directly acting sympathomimetic amines should also be used with caution although they are also metabolized by COMT and therefore are not subject to the same degree of exaggerated response.

MAOIs should be stopped for 2 weeks before starting alternative antidepressant therapy and 2 weeks should have elapsed from the end of tricyclic therapy to the start of MOAI therapy.

Atypical Agents:
Mianserin

Mianserin is a tetracyclic compound used in depressive illness, especially where sedation is required. It does not block the neuronal re-uptake of transmitters in

contrast to the TCAs. It does, however, block presynaptic a2-adrenoreceptors which reduces their negative feedback, resulting in increased synaptic concentrations of neurotransmitters.

It has very little ability to block muscarinic and peripheral a2-adrenoreceptors and as such causes less in the way of antimuscarinic effects or postural hypotension.

Its important side-effects are agranulocytosis and aplastic anaemia, which are more common in the elderly.

Lithium Carbonate

Lithium is used in the treatment of bipolar depression, mania and recurrent affective disorders. It has a narrow therapeutic index and plasma levels should be maintained at 0.51.5 mmol.l1. In excitable cells, lithium imitates Na+ and decreases the release of neurotransmitters.

It may increase generalized muscle tone and lower the seizure threshold in epileptics. Many patients develop polyuria and polydipsia due to antidiuretic hormone antagonism. It may also produce raised serum levels of Na+, Mg2+ and Ca2+. Lithium prolongs neuromuscular blockade and may decrease anaesthetic requirements as it blocks brain stem release of noradrenaline and dopamine.

The thyroid gland may become enlarged and underactive and the patient may experience weight gain and tremor. Above the therapeutic level patients suffer with vomiting, abdominal pain, ataxia, convulsions, arrhythmias and death.

Anticonvulsants

Where possible a single agent should be used to treat epilepsy as it avoids the potential for drug interaction. In addition patients rarely improve with a second agent.

Phenytoin

Uses

Phenytoin has been used widely for many years in the treatment of grand mal and partial seizures, trigeminal neuralgia and ventricular arrhythmias following TCA overdose. It may be given orally or intravenously but the dose must be tailored to the individual patient as wide interpatient variation exists (about 9% of the population are slow hydroxylators) and blood assays are useful in this regard. It is incompatible with 5% dextrose, in which it becomes gelatinous. The normal therapeutic level is 1020 µg.ml1.

Mechanism of Action

The action of phenytoin is probably dependent on its ability to bind to and stabilize inactivated Na+ channels. This prevents the further generation of action

potentials that are central to seizure activity. It may also reduce Ca2+ entry into neurones, blocking transmitter release and enhancing the actions of g-aminobutyric acid (GABA).

Effects

• Idiosyncraticacne, coarsening of facial features, hirsutism, gum hyperplasia, folate-dependent megaloblastic anaemia, aplastic anaemia, various skin rashes and peripheral neuropathy.

• Dose-relatedataxia, nystagmus, parasthesia, vertigo and slurred speech. Rapid undiluted intravenous administration is associated with hypotension and heart block.

• Teratogenicityit causes craniofacial abnormalities, growth retardation, limb and cardiac defects and mental retardation.

• Drug interactionsas phenytoin induces the hepatic mixed function oxidases it increases the metabolism of warfarin, benzodiazepines and the oral contraceptive pill. Its metabolism may be inhibited by metronidazole, chloramphenicol and isoniazid leading to toxic levels. Furthermore phenytoin's metabolism may be induced by carbamazepine or alcohol resulting in reduced plasma levels.

Kinetics

The oral bioavailability is approximately 90% and it is highly plasma protein-bound (90%). It undergoes saturable hepatic hydroxylation resulting in zero-order kinetics just above the therapeutic range. It can induce its own metabolism and that of other drugs. Its major metabolite is excreted in the urine.

Carbamazepine

Carbamazepine is also used in the treatment of trigeminal neuralgia. Its mode of action is similar to that of phenytoin. It may be given orally or rectally.

Effects

• Central nervous systemmild neurotoxic effects including headache, diplopia, ataxia, vomiting and drowsiness are common and often limit its use.

• Metabolicit may produce an antidiuretic effect leading to water retention.

• Miscellaneousdrug-induced hepatitis, rashes in 510% and rarely agranulocytosis.

• Teratogenicityit causes facial abnormalities, intrauterine growth retardation, microcephaly and mental retardation. The incidence increases with dose. Overall incidence is about 1/3002000 live births.

• Drug interactionsas carbamazepine induces hepatic enzymes it demonstrates many of the interactions seen with phenytoin. Levels of concurrently administered phenytoin may be elevated or reduced. Erythromycin can increase serum levels of carbamazepine.

Kinetics

Carbamazepine is well absorbed from the gut with a high oral bioavailability. It is approximately 75% plasma protein-bound and undergoes extensive hepatic metabolism to carbamazepine 10,11-epoxide, which retains about 30% of carbamazepine's anticonvulsant properties. It powerfully induces hepatic enzymes and induces its own metabolism. Its excretion is almost entirely in the urine as unconjugated metabolites.

Sodium Valproate

Uses

Sodium valproate is used in the treatment of various forms of epilepsy including absence (petit mal) seizures and in the treatment of trigeminal neuralgia.

Mechanism of Action

Sodium valproate appears to act by stabilizing inactive Na+ channels and also by stimulating central GABA-ergic inhibitory pathways. It is generally well tolerated.

Effects

• Abdominalit may cause nausea and gastric irritation. Pancreatitis and potentially fatal hepatotoxicity are recognized following its use.

• Haematologicalthrombocytopenia and reduced platelet aggregation.

• Miscellaneoustransient hair loss.

• Teratogenicityit causes neural tube defects.

Kinetics

Sodium valproate is well absorbed orally, highly protein-bound (approximately 90%) and undergoes hepatic metabolism to products (some of which are active) which are excreted in the urine.

Phenobarbitone is an effective anticonvulsant but its use is associated with significant sedation which limits its use. It is a long-acting barbiturate that induces

hepatic enzymes and interacts with other agents (warfarin, oral contraceptives, other anticonvulsants).

BDZs (see above) are widely used in the emergency treatment of status epilepticus and act by enhancing the chloride gating function of GABA.

Other Agents

Vigabatrin, gabapentin and lamotrigine are newer agents that are used in the control of persistent partial seizures.

Vigabatrin irreversibly inhibits GABA-transaminase, the enzyme responsible for the breakdown of GABA and therefore its duration of action is about 24 hours, while its elimination half-life is only 6 hours. It is excreted unchanged in the urine. It interacts with phenytoin reducing its concentration by about 25% by an unknown mechanism. It may cause sedation, fatigue, headache, agitation and depression.

Lamotrigine acts on the presynaptic neuronal membrane and stabilizes the inactive Na+ channel leading to a reduction in excitatory neurotransmitter release. It undergoes hepatic metabolism to an inactive conjugate. Its rate of metabolism is increased by other enzyme-inducing drugs (carbamazepine and phenytoin) but reduced by sodium valproate. It may precipitate headache, nausea, diplopia, ataxia and tremor. Approximately 0.1% of adults develop StevensJohnson or Lyell's syndrome. The incidence is higher in children.

Gabapentin's mode of action is uncertain but it may bind to Ca2+ channels within the brain. It is excreted unchanged in the urine and does not interfere with other anticonvulsants. It is well tolerated.

18
Antiemetics and Related Drugs

Nausea and vomiting has many causes including drugs, motion sickness, fear, pregnancy, vestibular disease and migraine. In previous decades anaesthesia was almost synonymous with vomiting, but with the advent of new anaesthetic agents and more aggressive treatment the incidence of vomiting has decreased. However, even the latest agents have failed to eradicate this troublesome symptom encountered in the peri-operative period.

Physiology

The vomiting centre (VC) coordinates vomiting. It has no discrete anatomical site but may be considered as a collection of effector neurones situated in the medulla. This collection projects to the vagus and phrenic nerves and also to the spinal motor neurones supplying the abdominal muscles, which when acting together bring about the vomiting reflex.

The VC has important input from the chemoreceptor trigger zone (CTZ) which lies in the area postrema on the floor of the fourth ventricle but is functionally outside the bloodbrain barrier. The CTZ is rich in dopamine (D2) receptors and also serotonin (5-HT) receptors. Acetylcholine (ACh) is important in neural transmission from the vestibular apparatus. Other input is summarized in Figure 18.1.

The treatment of nausea and vomiting is aimed at reducing the afferent supply to the VC. While the administration of antiemetics forms a vital part of treatment, attention should also be given to minimizing the administration of opioids by the use of non-steroidal anti-inflammatory drugs and avoiding unnecessary anticholinesterase administration. When propofol is used to maintain anaesthesia for minor surgery, where the use of opioids is limited, it may reduce the incidence of postoperative nausea and vomiting (PONV).

The following types of agents have been used:

- Dopamine antagonists

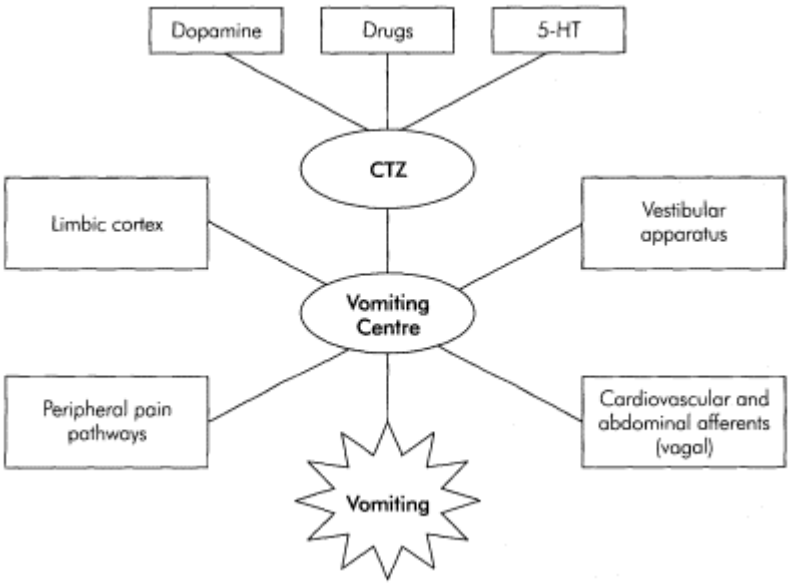


Figure 18.1:
Summary of the various neural inputs that result in vomiting.

- Anticholinergics
- Antihistamines
- 5-HT3 antagonists
- Miscellaneous

Dopamine Antagonists

1
Phenothiazines

Phenothiazines are the main group of anti-psychotic drugs (neuroleptics) and have only a limited role in the treatment of vomiting. They are divided into three groups on the basis of structure, which confers typical pharmacological characteristics (Table 18.1).

Table 18.1: Groups of Phenothiazines.

Propylamine	chlorpromazine
Piperidine	thioridazine
Piperazine	prochlorperazine, perphenazine

Chlorpromazine

Chlorpromazine's proprietary name 'Largactil' hints at the widespread effects of this drug.

Uses

Chlorpromazine is used in schizophrenia for its sedative properties and to correct altered thought. Its effects on central neural pathways are complicated but are thought to involve isolating the reticular activating system from its afferent connections. This results in sedation, disregard of external stimuli and a reduction in motor activity (neurolepsy). It is sometimes used to control vomiting or pain in terminal care where other agents have been unsuccessful. It has also been shown to be effective in preventing PONV. It is occasionally used to treat hiccup.

Mechanism of Action

Chlorpromazine antagonizes the following receptor types: dopaminergic (D2), muscarinic, noradrenergic (a1 and a2), histaminergic (H1) and serotinergic (5-HT). It also has membrane-stabilizing properties and prevents noradrenaline uptake into sympathetic nerves (uptake 1).

Effects

• Central nervous systemextrapyramidal effects are due to central dopamine antagonism. The neuroleptic malignant syndrome occurs rarely. It has variable effects on hypothalamic function, reducing the secretion of growth hormone while increasing the release of prolactin (dopamine functions as prolactin release inhibitory factor). Temperature regulation is altered and may result in hypothermia.

• Cardiovascularit antagonizes a-adrenoreceptors resulting in peripheral vasodilation, hypotension and increased heat loss.

• Anticholinergicit has moderate anticholinergic effects.

• Gutappetite is increased and patients tend to gain weight (exacerbated by inactivity). While it has been shown to be an adequate antiemetic its other effects have limited this role.

• Miscellaneouscontact sensitization. Direct contact should be avoided unless actually taking chlorpromazine. Cholestatic jaundice, agranulocytosis, leucopenia, leucocytosis, haemolytic anaemia are all recognized.

Kinetics

Absorption from the gut is good but due to a large hepatic first-pass metabolism (limiting its oral bioavailability to about 30%), it is often given parenterally. The large number of hepatic metabolites is excreted in the urine or bile, while a variable but small fraction is excreted unchanged in the urine.

Table 18.2: Effects of some dopamine antagonists.

	Chlorpromazine	Thioridazine	Prochlorperazine
Sedation	+ + +	+ +	+
Anticholinergic effects	+ +	+ + +	+
Extrapyramidal effects	+ +	+	+ + +

Thioridazine

Thioridazine is not used to treat nausea and vomiting. It is used in schizophrenia and other psychoses where it is favoured in the elderly as it is only moderately sedative and is only rarely associated with extrapyramidal effects (Table 18.2).

Prochlorperazine

Uses

Prochlorperazine is effective in the prevention and treatment of PONV and vertigo, as well as in schizophrenia and other psychoses.

Effects

• Central nervous systemextrapyramidal effects are seen more commonly in this class of phenothiazine. Acute dystonias and akathisia seem to be the most commonly encountered effects. Children and young adults are the most affected groups. When used peri-operatively it produces only mild sedation and may prolong the recovery time but the effects are not marked.

• Group specificin common with other phenothiazines prochlorperazine may cause cholestatic jaundice, haematological abnormalities, skin sensitization, hyperprolactinaemia and rarely the neuroleptic malignant syndrome.

Kinetics

Absorption by the oral route is erratic and the oral bioavailability is very low due to an extensive hepatic first-pass metabolism. It may be given by suppository, intravenous or intramuscular injection.

Perphenazine has similar indications and kinetics to prochlorperazine, and has been shown to be effective in the prevention and treatment of PONV. It is associated with a higher incidence of extrapyramidal effects and increased postoperative sedation than prochlorperazine.

2
Butyrophenones:
Droperidol

Droperidol is the only butyrophenone that is commonly used in anaesthetic practice.

Uses

Droperidol has been shown to be effective in the prevention and treatment of PONV at doses from 0.25 to 5 mg, although the incidence of side-effects increases with dose. It is also used in neurolept analgesia and in the control of mania.

Mechanism of Action

Droperidol antagonizes central dopamine (D2) receptors at the CTZ.

Effects

These are similar to those seen with phenothiazines.

- Central nervous systemsedation is more pronounced compared with the phenothiazines. The true incidence of extrapyramidal effects is unknown but increases with higher doses. They may develop more than 12 hours after administration and up to 25% of patients may experience anxiety up to 48 hours after administration. In sufficient dose it induces neurolepsis.

- Metabolicit may cause hyperprolactinaemia.

- Cardiovascularhypotension resulting from peripheral a adrenoreceptor blockade may occur.

Kinetics

Droperidol is usually given intravenously although it is absorbed readily after intramuscular injection. It is highly plasma protein-bound (approximately 90%) and extensively metabolized in the liver to products that are excreted in the urine, only 1% as unchanged drug.

Domperidone

This D2 antagonist is less likely to cause extrapyramidal effects as it does not cross the bloodbrain barrier. Its use in children is limited to nausea and vomiting following chemotherapy or radiotherapy. It also increases prolactin levels and may cause galactorrhoea and gynaecomastia. The intravenous preparation was withdrawn following serious arrhythmias during the administration of large doses. It is only available as tablets or suppositories.

3
Benzamides:
Metoclopramide

Uses

Metoclopramide is used as an antiemetic and a prokinetic. Approximately half of the clinical studies have demonstrated placebo to be as effective as metoclopramide as an antiemetic. However, metoclopramide appears to be most effective when 20 mg is given at the end of anaesthesia rather than at induction.

Mechanism of Action

Metoclopramide exerts its antiemetic actions primarily through dopamine (D2) receptor antagonism at the CTZ although it does have prokinetic effects on the stomach (cf. Chapter 19). It also blocks 5-HT3 receptors, which may account for some of its antiemetic properties.

Effects

• Central nervous systemmetoclopramide crosses the bloodbrain barrier and may precipitate extrapyramidal effects up to 72 hours after administration. Such effects are more common in young females (1 in 5000). Rarely it may precipitate the neuroleptic malignant syndrome. Sedation is seen more commonly during long-term administration. Agitation is occasionally seen following intramuscular premedication with 1020 mg.

• Cardiovascularhypotension, tachy- and bradycardias have been reported following rapid intravenous administration.

Kinetics

Metoclopramide is well absorbed from the gut although first-pass metabolism varies significantly producing a wide range in oral bioavailability (3090%). It may be given intravenously. It is conjugated in the liver and excreted along with unchanged drug in the urine.

Anticholinergics

While so called 'anticholinergic' agents are effective antagonists at muscarinic receptors they have very little activity at nicotinic receptors and may therefore be thought of as essentially selective agents at normal doses.

The naturally occurring tertiary amines, atropine and hyoscine, are esters formed by the combination of tropic acid and an organic base (tropine or scopine) and are able to cross the bloodbrain barrier. Their central effects include sedation, amnesia, anti-emesis and the central anticholinergic syndrome. Glycopyrrolate is a synthetic quaternary amine with no central effects as it is unable to cross the bloodbrain barrier.

Hyoscine

Hyoscine is a racemic mixture, but only L-hyoscine is active.

Uses

Hyoscine has traditionally been given with an intramuscular opioid as premedication, and in this setting has been shown to reduce PONV. It has also been used as a sedative and amnesic agent.

Effects

While its main uses are derived from its central antimuscarinic effects it also has peripheral antimuscarinic effects some of which can be useful and are summarized in Table 18.3.

Other central effectsit may precipitate a central anticholinergic syndrome, which is characterized by excitement, ataxia, hallucinations, behavioural abnormalities and drowsiness.

Kinetics

When given orally its absorption is variable so that its oral bioavailability lies between 10 and 50%. Transdermal administration is effective in reducing PONV and motion sickness despite very low plasma levels. It is extensively metabolized by liver esterases and only a small fraction is excreted unchanged in the urine. Its duration of action is shorter than that of atropine.

Atropine

Atropine is a racemic mixture, but only L-atropine is active.

Uses

Atropine is used to treat bradycardia and as an anti-sialagogue. It is also used to antagonize the muscarinic side-effects of anticholinesterases. It is not used to treat PONV because of its cardiovascular effects.

Effects

• Central nervous systemit is less likely to cause a central cholinergic crisis than hyoscine and is less sedative.

• Cardiovascularit may cause an initial bradycardia following a small intravenous dose. This may be due to its effects centrally on the vagal nucleus or reflect a partial agonist effect at cardiac muscarinic receptors.

• Respiratory systembronchodilation is more marked than with hyoscine, leading to an increase in dead space. Bronchial secretions are reduced.

• Gutit is a less effective anti-sialagogue than hyoscine. The tone of the lower oesophageal sphincter is decreased and there is a small decrease in gastric acid secretion.

• Miscellaneoussweating is inhibited and this may provoke a pyrexia in paediatric patients. When administered topically it may increase intraoccular pressure, which may be critical for patients with glaucoma.

Table 18.3: Effects of some anticholinergics.

	Hyoscine	Atropine	Glycopyrrolate
Antiemetic potency	+ +	+	0
Sedation/amnesia	+ + +	+	0
Anti-sialagogue	+ + +	+	+ +
Mydriasis	+ + +	+	0
Placental transfer	+ +	+ +	0
Bronchodilation	+	+ +	+ +
Heart rate	+	+ + +	+ +

Kinetics

Intestinal absorption is rapid but unpredictable. It is 50% plasma protein-bound and extensively metabolized by liver esterases. It is excreted in the urine, only a tiny fraction unchanged.

Glycopyrrolate

Gylcopyrrolate is indicated for anti-sialagogue premedication, the treatment of bradycardias and to protect against the unwanted effects of anticholinesterases. Its quaternary structure prevents it from crossing the bloodbrain barrier and so it is devoid of central effects. Its kinetics are somewhat different from the tertiary amines in this class of drugs. Intestinal absorption is negligible and the oral bioavailability is consequently less than 5%. It is minimally metabolized and 80% is excreted in the urine unchanged.

Antihistamines

Cyclizine

Cyclizine is a piperazine derivative. The parenteral preparation is prepared with lactic acid at pH 3.2. Consequently intramuscular and intravenous injection may be particularly painful.

Uses

Cyclizine is used as an antiemetic in motion sickness, radiotherapy, PONV and emesis induced by opioids. It is also used to control the symptoms of Ménière's disease.

Mechanism of Action

Cyclizine is a histamine (H1) antagonist, but also has anticholinergic properties that may contribute significantly to its antiemetic actions.

Effects

- Gutit increases lower oesophageal sphincter tone.
- Anticholinergicthese are mild although it may cause a slight increase in heart rate following intravenous injection.
- Extrapyramidal effects and sedation do not complicate its use.

Kinetics

Cyclizine is well absorbed orally and has a high oral bioavailability (approximately 75%). Surprisingly little is known regarding the rest of the kinetics of this drug.

Promethazine

Promethazine has traditionally been used in combination with pethidine for intramuscular premedication. However, it may also be used as an oral premed for children. It has significant anticholinergic properties and sedative effects. It is well absorbed from the gut but is subject to a significant first-pass hepatic metabolism so that its oral bioavailability is 25%. It has a duration of action of 36 hours and its metabolites are eliminated entirely in the urine.

5-HT3 Antagonists

Ondansetron

Ondansetron is a carbazole.

Presentation

Ondansetron is available as tablets (48 mg), a strawberry-flavoured lyophilisate (48 mg) to dissolve on the tongue, a suppository (16 mg) and as a clear solution containing 2 mg.ml1 for slow intravenous injection.

Uses

Ondansetron is indicated for the treatment of nausea and vomiting associated with chemo- or radiotherapy and in the peri-operative period. It is ineffective for vomiting induced by motion sickness or dopamine agonists. It is licensed for children above 2 years of age.

Mechanism of Action

The activation of 5-HT3 receptors peripherally and centrally appears to induce vomiting. Chemo- and radiotherapy may cause the release of 5-HT from enterochromaffin cells. Peripheral 5-HT3 receptors in the gut are then activated and stimulate vagal afferent neurones that connect to the VC, again via 5-HT3 receptors. Thus ondansetron may antagonize 5-HT3 both peripherally and centrally.

Effects

Ondansetron is well tolerated and its other effects are limited to headache, flushing, constipation and bradycardia following rapid intravenous administration.

Kinetics

Ondansetron is well absorbed from the gut with an oral bioavailability of about 60%. It is 75% protein-bound and undergoes significant hepatic metabolism by hydroxylation and subsequent glucuronide conjugation to inactive metabolites. Its half-life is 3 hours. The dose should be reduced in hepatic impairment.

While ondansetron clearly has a place in the treatment of nausea and vomiting it has not universally been shown to be superior to low dose droperidol or a phenothiazine. This together with its higher cost suggests it should be used only when conventional therapy is expected to, or has failed.

Miscellaneous

Acupuncture

Several studies have demonstrated the effectiveness of acupuncture in the prevention of PONV. The acupuncture point lies between the tendons of flexor carpi radialis and palmaris longus about 4 cm from the distal wrist skin crease. It should be performed on the awake patient and is free from side-effects.

Canabinoids

Nabilone acts at the VC and has been used as an antiemetic following chemotherapy.

Benzodiazepines

Lorazepam is used as an antiemetic during chemotherapy. It has amnesic and sedative properties. Its mode of action as an antiemetic is uncertain but it may modify central connections to the VC and prevent the anticipatory nausea that is seen with repeated doses of chemotherapy.

Steroids

Intravenous dexamethasone has been used as an antiemetic during chemotherapy. Its mode of action is uncertain but it does appear to be effective.

19
Drugs Acting on the Gut

- Antacids
- Drugs influencing gastric secretion
- Drugs influencing gastric motility
- Mucosal protectors
- Prostaglandin analogues

Antacids

Antacids neutralize gastric acidity. They are used to relieve the symptoms of dyspepsia and gastro-oesophageal reflux. They promote ulcer healing, but less effectively than other therapies.

Aluminium- and Magnesium-Containing Antacids

Neither is absorbed from the gut significantly and due to their relatively low water solubility they are long-acting providing that they remain in the stomach. Aluminium-containing antacids have a slower action and produce constipation, while magnesium-containing antacids produce diarrhoea. Aluminium ions form complexes with some drugs (e.g. tetracycline) and reduce their absorption.

Sodium Bicarbonate and Sodium Citrate

These antacids are water-soluble and their onset of action is faster than the aluminium- and magnesium-containing antacids. They are absorbed into the systemic circulation and may cause a metabolic alkalosis if taken in excess. Sodium bicarbonate releases carbon dioxide as it reacts with gastric acid, resulting in belching. 30 ml of 0.3 M sodium citrate is often used with ranitidine to reduce gastric acidity before caesarean section. It should be given less than 10 minutes before the start of surgery due to its limited duration of action.

Drugs Influencing Gastric Secretion

Physiology

Gastrin and acetylcholine (ACh) stimulate parietal cells (via gastrin and muscarinic receptors) to secrete H+ into the gastric lumen. ACh is released from parasympathetic postganglionic fibres while gastrin is released from G-cells in the antral mucosa. However, the main stimulus for parietal cell acid secretion is via histamine receptor activation. Gastrin and ACh also stimulate the adjacent paracrine cells to produce and release histamine, which acts on the parietal cell, increasing cAMP and therefore acid secretion.

H2 Receptor Antagonists:
Cimetidine

Cimetidine is the only H2 receptor antagonist with an imidazole structure.

Uses

It is used in peptic ulcer disease, reflux oesophagitis, ZollingerEllison syndrome and pre-operatively in those at risk of aspiration. It has not been shown to be of benefit in active haematemesis, although it does have a prophylactic role in those with critical illness.

Mechanism of Action

Cimetidine is a competitive and specific antagonist of H2 receptors at parietal cells.

Effects

• Gutthe gastric pH is raised and the volume of secretions reduced, while there is no change in gastric emptying time or lower oesophageal sphincter tone.

• Cardiovascularbradycardia and hypotension follow rapid intravenous administration.

• Central nervous systemconfusion, hallucinations and seizures are usually only seen when impaired renal function leads to high plasma levels.

• Respiratory systemlow grade aspiration of gastric content that has been stripped of its acidic, antibacterial environment will result in increased nosocomial pulmonary infections in critically ill ventilated patients.

• Endocrinegynaecomastia, impotence and a fall in sperm count is seen in men due to its anti-androgenic effects.

• Metabolicit inhibits hepatic cytochrome P450 and will slow the metabolism of the following drugs: lignocaine, propranolol, diazepam, phenytoin, tricyclic antidepressants, warfarin and aminophylline.

Kinetics

Cimetidine is well absorbed from the small bowel (oral bioavailability approximately 60%), poorly plasma protein-bound (20%), partially metabolized (up to 60% if administered orally) in the liver by cytochrome P450 and approximately 50% excreted unchanged in the urine.

Ranitidine

Ranitidine is more potent than cimetidine.

Uses

Ranitidine has similar uses to cimetidine. However, because it does not inhibit hepatic cytochrome P450 it is often used in preference to cimetidine. It is used in combination with antibiotics to eradicate *H. pylori.* It is also used widely in labour with apparently no deleterious effects on the foetus or progress of labour.

Mechanism of Action

Similar to that of cimetidine.

Effects

• Gutsimilar to that of cimetidine.

• Cardiovascularit may produce cardiac arrhythmias during rapid intravenous administration.

• Metabolicit should be avoided in porphyria, although reports detailing this interaction are inconclusive. It has no anti-androgenic effects.

• Miscellaneousrarely it may cause thrombocytopenia, leucopenia, reversible abnormalities of liver function and anaphylaxis.

Kinetics

Ranitidine is well absorbed from the gut, poorly protein-bound (15%) and partially metabolized in the liver. It undergoes a greater degree of first-pass metabolism than cimetidine (oral bioavailability approximately 50%), while 50% of an administered dose is excreted unchanged in the urine.

Nizatidine and famotidine are newer H2 antagonists with increased potency. Like ranitidine they do not inhibit hepatic cytochrome P450.

Proton Pump Inhibitors:
Omeprazole

Uses

Omeprazole is used for similar indications to that of ranitidine but also in cases where H2 blockade is insufficient. It may be given orally or intravenously.

Mechanism of Action

A proton pump (K+/H+ ATPase) in the membrane of the parietal cell mediates the final common pathway of gastric acid secretion. Omeprazole reversibly blocks the proton pump and so achieves complete achlorhydria.

Effects

• Gutthe acidity and volume of gastric secretions is reduced, while no change is seen in lower oesophageal sphincter tone or gastric emptying.

• Metabolicinhibition of hepatic cytochrome P450. This is limited and although close monitoring is recommended with concurrent use of warfarin and phenytoin their effects are rarely potentiated. The effects of diazepam may be increased via a similar mechanism.

• Miscellaneousrashes and gastrointestinal upset are rare.

Kinetics

Omeprazole is degraded in gastric acid and so is prepared as a capsule with enteric-coated granules so that absorption occurs in the small intestine. It is a prodrug, becoming active within the parietal cell. It undergoes complete hepatic metabolism by cytochrome P450 to inactive metabolites which are excreted in the urine (80%) and bile (20%).

Lansoprazole may be considered as an alternative to omeprazole.

Antimuscarinics

Pirenzipine is a selective antimuscarinic that was used in the treatment of gastric ulcers. It is relatively selective on the gut and decreases acid secretion, but less effectively than H2 blockers and the proton pump inhibitors. Its use has been discontinued.

Drugs Influencing Gastric Motility

Metoclopramide

Metoclopramide is a dopamine antagonist with structural similarities to procainamide although it has no local anaesthetic properties.

Uses

Metoclopramide is used as a prokinetic and an antiemetic (see Chapter 18).

Mechanism of Action

Its prokinetic actions are mediated by antagonism of peripheral dopaminergic (D2) receptors and selective stimulation of gastric muscarinic receptors (which can be blocked by atropine).

Effects

• Central nervous systemextrapyramidal effects, the most common manifestations of which are akinesia and occulogyric crisis, are only seen when metoclopramide is given in high doses, renal impairment, the elderly and the young. They can be treated with the anticholinergic agent benztropine. Metoclopramide may cause some sedation and enhance the actions of antidepressants. The neuroleptic malignant syndrome may also be triggered. Its central effects on the chemoreceptor trigger zone are discussed in Chapter 18.

• Gutits peripheral actions result in an increased lower oesophageal sphincter tone and relaxation of the pylorus. It has no effect on gastric secretion.

• Cardiovascularacute conduction abnormalities follow rapid intravenous administration, and acute hypertension occurs in phaeochromocytoma.

• Metabolicit may precipitate hyperprolactinaemia and galactorrhoea, and should be avoided in porphyria. It inhibits plasma cholinesterase activity in vitro, and may therefore prolong the effects of drugs metabolized by this enzyme.

Kinetics

Metoclopramide is well absorbed from the gut although first-pass metabolism varies significantly producing a wide range in oral bioavailability (3090%). It may be given intravenously. It is conjugated in the liver and excreted along with unchanged drug in the urine.

Domperidone

This dopamine antagonist is less likely to cause extrapyramidal effects as it does not cross the bloodbrain barrier. Its use in children is limited to nausea and vomiting following chemotherapy or radiotherapy. It also increases prolactin levels and may cause galactorrhoea and gynaecomastia. The intravenous preparation was withdrawn following serious arrhythmias during administration of large doses. It is only available as tablets or suppositories.

Cisapride

Uses

Its main indications are in symptom management of reflux, dyspepsia and gastroparesis (secondary to opioids or autonomic neuropathy). It has no antiemetic effects.

Mechanism of Action

Cisapride appears to enhance the release of ACh from the nerve endings of the mesenteric plexus within the gut wall. This can be reversed by anticholinergics. It has no dopaminergic effects.

Effects

• Cardiovascularcertain drugs (azole antifungals; fluclonazole, itraconazole, ketoconazole: certain antibiotics; erythromycin and clarithromycin: protease inhibitors; ritonavir and indinavir) inhibit its metabolism, resulting in excessively high plasma levels. This may prolong the QT interval and precipitate serious arrhythmias including torsades de pointes. There is also evidence that therapeutic concentrations have electrophysiological effects on the heart.

• Gutthe lower oesophageal sphincter pressure is increased and motility is increased in the stomach, small and large bowel leading to cramps, diarrhoea and borborygmi.

• Central nervous systemconvulsions and extrapyramidal effects have been reported.

Kinetics

Cisapride is rapidly absorbed and extensively bound to plasma proteins (mainly albumin). It undergoes significant first-pass metabolism in the gut wall and by hepatic cytochrome P450 (3A4). The metabolites are excreted in urine and faeces. Its kinetics are unpredictable and it is specifically contraindicated in premature infants and for up to 3 months after birth.

Mucosal Protectors

Sucralfate

Sucralfate exerts a generalized cytoprotective effect by forming a barrier over the gut lumen. It protects ulcerated regions specifically. It does not alter gastric pH, motility or lower oesophageal sphincter tone although it has been reported to have bacteriostatic effects.

Its actions are due to its local effects and virtually none is absorbed from the gut. Consequently it has no effect on the central nervous or cardiorespiratory systems.

Effects

• Gutminor gastric disturbances. Enhanced aluminium absorption in patients with renal dysfunction or on dialysis. It may reduce the absorption of certain drugs (ciprofloxacin, warfarin, phenytoin, and H2 antagonists) by direct binding.

Prostaglandin Analogues

Misoprostil

Misoprostil is a synthetic analogue of prostaglandin E1.

Uses

It is used for the prevention and treatment of non-steroidal anti-inflammatory induced ulcers.

Mechanism of Action

It inhibits gastric acid secretion and increases mucous secretion thereby protecting the gastric mucosa.

Effects

• Endocrineit increases uterine tone and may precipitate miscarriage. Menorrhagia and vaginal bleeding have been reported.

• Gutsevere diarrhoea and other intestinal upset.

• Cardiovascularat normal doses it is unlikely to produce hypotension but its use is cautioned where hypotension could precipitate severe complications (i.e. in cerebrovascular or cardiovascular disease).

Kinetics

Misoprostil is rapidly absorbed from the gut. Metabolism is by fatty acid-oxidizing systems throughout the body and no alteration in dose is required in renal or hepatic impairment.

20
Diuretics

The kidney is a complex organ maintaining fluid, electrolyte and acidbase balance. It also serves an endocrine function by secreting renin and erythropoietin. Diuretics are drugs that act on the kidney to increase urine production and can be divided into the following groups:

- thiazides
- loop diuretics
- potassium sparing
- aldosterone antagonists
- osmotic
- carbonic anhydrase inhibitors

Thiazides (Bendrofluazide, Chlorothiazide, Metolazone)

Uses

Thiazides (which are chemically related to the sulphonamides) are widely used in the treatment of mild heart failure and hypertension, alone or in combination with other drugs. They have also been used in diabetes insipidus where they may increase the sensitivity of the collecting ducts to remaining antidiuretic hormone (ADH) or cause Na+ depletion and therefore reduced water absorption in the proximal tubule. In addition, they have been used in renal tubular acidosis. The main difference between the drugs is their rate of absorption from the gut due to differences in lipid solubility and rate of onset and duration of action due to differences in handling by the renal tubule.

Mechanism of Action

Thiazides are moderately potent and act mainly on the early segment of the distal tubule by inhibiting Na+ and Cl reabsorption. This leads to increased Na+ and

Cl excretion and therefore increased water excretion. The increased Na+ load reaching the distal tubule stimulates an exchange with K+ and H+ so that thiazides tend to precipitate a hypokalaemic, hypochloraemic alkalosis. Thiazides also reduce carbonic anhydrase activity resulting in an increased bicarbonate excretion, however this effect is small and of little clinical significance.

Metolazone has very powerful synergistic effects when combined with a loop diuretic and is useful in cases of renal failure.

Effects

- Cardiovascularthiazides appear to produce their antihypertensive effect by a reduction in plasma volume and systemic vascular resistance which is maximally achieved at low dose.

- Renalthey reduce renal blood flow and may cause a reduction in glomerular filtration rate.

- Biochemicaltheir actions on the kidney lead to various biochemical imbalances. Hypokalaemia may provoke dangerous arrhythmias in those patients taking digoxin concurrently, although oral K+ supplements usually maintain plasma levels within normal limits. Combination with a K+ sparing diuretic may help to control plasma K+. Hypercalcaemia may result from reduced renal Ca2+ excretion. Thiazides may also precipitate a hypochloraemic alkalosis, hyponatraemia and hypomagnesaemia. Thiazides and uric acid are secreted by the same mechanism within the renal tubules. This competition leads to reduced uric acid excretion and a rise in plasma levels which may precipitate gout.

- Metabolicreduced glycogenesis and insulin secretion, coupled with enhanced glycogenolysis tends to raise plasma glucose levels. These effects are most noticeable in diabetic patients. Thiazides increase plasma cholesterol and triglyceride levels.

- Haematologicalvarious blood dyscrasias are occasionally seen, and include aplastic and haemolytic anaemia, leucopenia, agranulocytosis and thrombocytopenia.

- Miscellaneousimpotence, rash and photosensitivity occur rarely. Bendrofluazide may precipitate pancreatitis.

- Interactionsthe hypokalaemia produced by thiazides may prolong the duration of action of non-depolarizing muscle relaxants. Non-steroidal anti-inflammatory drugs (NSAIDs) antagonize the effects of thiazides.

Kinetics

Bendrofluazide is well absorbed from the gut in contrast with chlorothiazide, which is incompletely and variably absorbed. They both produce effects within 90 minutes of oral administration although bendrofluazide has twice the duration of action at 1824 hours. The lower lipid solubility of chlorothiazide results in elimination solely via the kidneynone being metabolized, unlike bendrofluazide which is 70% metabolized in the liver to active metabolites, the rest being eliminated unchanged in the urine.

Loop Diuretics (Frusemide, Bumetanide)

Uses

Loop diuretics (carboxylic acid derivatives) are used in severe heart failure to reduce peripheral and pulmonary oedema. They are also used in chronic and acute renal failure.

Mechanism of Action

Loop diuretics inhibit Na+ and Cl reabsorption in the thick ascending limb of the loop of Henle and to a lesser extent in the early part of the distal tubule. This impairs the action of the counter-current multiplier system and reduces the hypertonicity of the medulla which reduces reabsorption of water in the collecting system. The thick ascending part of the loop of Henle has a large capacity for NaCl reabsorption so when ion reabsorption is blocked the effects are marked.

Effects

• Cardiovascularlike thiazides they produce arteriolar vasodilatation which reduces systemic vascular resistance. The preload is also reduced ahead of any change that could be attributed to a diuresis.

• Renalin contrast with the thiazides an increase in renal blood flow is seen with blood being diverted from the juxtaglomerular region to the outer cortex.

• Biochemicalthe disturbances seen are similar to those induced by the thiazides and include hyponatraemia, hypokalaemia, hypomagnesaemia, and a hypochloraemic alkalosis. In contrast with the thiazides the loop diuretics may precipitate hypocalcaemia due to increased Ca2+ excretion. Hyperuricaemia is sometimes seen and occasionally precipitates gout.

• Metabolichyperglycaemia is less common than with thiazides. Loop diuretics increase plasma cholesterol and triglyceride levels although these usually return to normal during long-term treatment.

• Miscellaneousdeafness occasionally follows rapid administration of a large dose and is more common in patients with renal failure, and those on aminoglycoside therapy. Bumetanide is less ototoxic than frusemide but may also cause myalgia.

• Interactionslithium levels may rise when given with loop diuretics.

Kinetics

Both frusemide and bumetanide are well absorbed from the gut although their oral bioavailability is different (65% and 95% respectively). Both drugs are highly plasma protein bound (> 95%) and excreted largely unchanged in the urine.

Potassium Sparing (Amiloride)

Uses

Amiloride is a weak diuretic that is frequently used in combination with loop diuretics to prevent hypokalaemia.

Mechanism of Action

At the distal convoluted tubule it blocks Na+/K+ exchange, creating a diuresis, and decreasing K+ excretion.

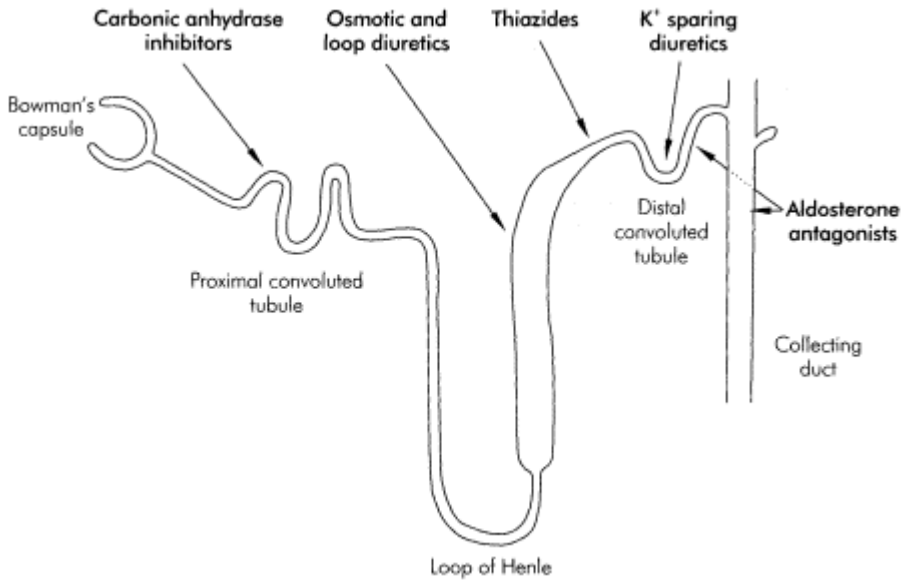


Figure 20.1:
Main sites of action of the diuretics.

Effects

• Metabolichyperkalaemia may sometimes follow its use. The hypokalaemic, hypochloraemic metabolic alkalosis seen with thiazide and loop diuretics is not a feature of K+ sparing diuretics.

Kinetics

Amiloride is poorly absorbed from the gut, minimally protein bound and not metabolized.

Aldosterone Antagonists (Spironolactone)

Spironolactone is only available as an oral preparation. Potassium canrenoate is available parenterally and is metabolized to canrenone which is also a metabolite of spironolactone.

Uses

Owing to its mode of action its effects take a few days to become established. It is used to treat ascites, nephrotic syndrome and primary hyperaldosteronism (Conn's syndrome).

Mechanism of Action

Spironolactone is a competitive aldosterone antagonist. Normally aldosterone stimulates the reabsorption of Na+ in the distal tubule, which provides the driving force for the excretion of K+. When aldosterone is antagonized, K+ excretion is significantly reduced while increased Na+ excretion produces a diuresis. The diuresis produced is limited as only 2% of Na+ reabsorption is under the control of aldosterone.

Effects

• Biochemicalhyperkalaemia is most common in patients with renal impairment. Angiotensin-converting enzyme (ACE) inhibitors also predispose to hyperkalaemia because they reduce aldosterone secretion. It may also produce hyponatraemia.

• Hormonalgynaecomastia in men and menstrual irregularity in women are seen due to spironolactone's anti-androgenic effects. It is contraindicated in Addison's disease.

Kinetics

Spironolactone is incompletely absorbed from the gut and highly protein bound. It is rapidly metabolized and excreted in the urine.

Osmotic (Mannitol)

The carbohydrate derivative mannitol is a polyhydric alcohol.

Uses

Mannitol is used to reduce intracranial pressure (ICP) in the presence of cerebral oedema or during neurosurgery. It is also used to preserve peri-operative renal function in the jaundiced patient and those undergoing major vascular surgery. It is prepared in water as a 10 or 20% solution. For the treatment of raised ICP the initial dose is 1 g.kg1, which is then reduced to 0.10.2 g.kg1. However, if the serum osmolality rises above 320 mosm.kg1, further doses of mannitol should not be given due to an increased risk of renal failure.

Mechanism of Action

Mannitol is freely filtered at the glomerulus but not reabsorbed in the tubules. It increases the osmolality of the filtrate so that by an osmotic effect the volume of urine is increased. It is unable to pass through an intact bloodbrain barrier and by virtue of an increased plasma osmolality it draws extracellular brain water into the plasma. However, a head injury may give rise to a damaged bloodbrain barrier. In this situation mannitol traverses the bloodbrain barrier and will drag water with it, thereby increasing cerebral oedema.

Effects

- Cardiovascularinitially circulating volume is increased producing an increased preload and cardiac output. In susceptible patients this may precipitate heart failure.

- Renalit produces an osmotic diuresis and increased renal blood flow that may result in a reduced intravascular volume.

- Central nervous systemit produces an acute reduction in ICP which is not sustained during prolonged administration. It may also reduce the rate of formation of cerebrospinal fluid.

- Allergicthese responses occur rarely.

Kinetics

Mannitol is minimally absorbed from the gut. Following intravenous administration mannitol is distributed throughout the extracellular fluid space. It is freely filtered at the glomerulus and not reabsorbed, resulting in an elimination half-life of 100 minutes. It is not metabolized to any significant extent.

Carbonic Anhydrase Inhibitors (Acetazolamide)

Acetazolamide is a weak diuretic and is only rarely used as such.

Uses

Acetazolamide is used as prophylaxis against mountain sickness by partially reversing the respiratory alkalosis with a metabolic acidosis. Eye drops inhibit aqueous humour production and it is useful in the treatment of glaucoma.

Mechanism of Action

Acetazolamide inhibits (non-competitively) carbonic anhydrase which catalyses the formation of H+ and HCO3 from CO2 and H2O in the proximal tubule.

Effects

• BiochemicalH+ excretion is inhibited and HCO3 is not reabsorbed leading to an alkaline urine. Na+ and water excretion are slightly increased providing an increased drive for K+ secretion. Therefore, it produces an alkaline urine in the presence of a hyperchloraemic acidosis.

Kinetics

Acetazolamide has an oral bioavailability of more than 95%, is highly protein bound and is excreted unchanged in the urine.

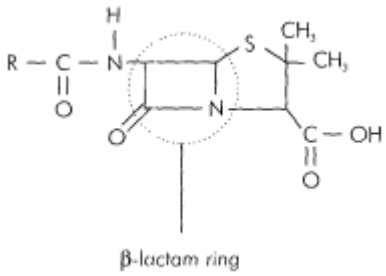
21
Antimicrobials

Antimicrobial agents are used to kill or suppress the growth of microorganisms. Antibacterial agents have more specific actions against bacteria while antibiotic refers to a chemical substance that is produced by a microorganism, which has the capacity to kill or inhibit the growth of another microorganism. The following headings are used to discuss the various antimicrobials

- Antibacterial drugs
- Antifungal drugs
- Antiviral drugs

Antibacterial Drugs

1
Penicillins



Uses

Penicillins remain useful and effective antimicrobial agents despite their relatively narrow spectrum of activity against Gram-positive organisms.

Mechanism of Action

They are bactericidal, inhibiting bacterial cell wall synthesis by combining with the transpeptidase used to cross link cell wall peptidoglycan. This activity depends on

an intact b-lactam ring, whose structure resembles part of the peptide chains of the bacterial cell wall. However, the b-lactam ring may be split open by the bacterial enzyme b-lactamase (penicillinase), rendering it ineffective.

Kinetics

Intestinal absorption is variable and certain penicillins are only available as parenteral preparations. Tissue penetration is generally good although they only pass through the bloodbrain barrier when the meninges are inflamed. Excretion is largely in the urine as unchanged drug. Probenecid blocks active tubular secretion, producing higher and more prolonged plasma concentrations.

Specific Penicillins

• *Benzylpenicillin and Phenoxymethylpenicillin*

Benzylpenicillin (penicillin G) is inactivated by gastric acid and must, therefore, be given by injection. Phenoxymethylpenicillin (penicillin V) is stable in acidic conditions but intestinal absorption is unreliable and so it is not recommended for serious infections as it is not available as a parenteral formulation.

· b-*Lactam resistance*

Most staphylococci are resistant to benzylpenicillin due to b-lactamase production. However, the semi-synthetic penicillin flucloxacillin is not affected by b-lactamase and, therefore, it provides effective therapy in this setting. It is well absorbed from the gut but should be given intravenously for serious infections. It may cause cholestatic jaundice several weeks after the end of a course of treatment.

• *Broad spectrum*

Ampicillin and its derivative amoxycillin are effective against certain Gram-positive and Gram-negative organisms due to better penetration of the bacterial cell wall. However, both are inactivated by b-lactamase. Clavulinic acid is an irreversible inhibitor of most b-lactamases and when combined with amoxycillin as Co-Amoxiclav it provides useful activity against amoxycillin-resistant organisms (i.e. 90% of *staphylococci*, 50% *E. coli* and 15% *H. influenzae* as well as many *Bacteroides* and *Klebsiella*). For oral administration amoxycillin is preferred due to better intestinal absorption. Clavulinic acid may be responsible for the rare occurrence of cholestatic jaundice several weeks after treatment has been stopped.

• *Anti-pseudomonal penicillins*

The carboxypenicillin ticarcillin and the ureidopenicillins azlocillin and piperacillin have a broad spectrum but are particularly indicated for use against *Pseudomonas.* Ticarcillin has been combined with clavulinic acid and piperacillin with tazobactam (both b-lactamase inhibitors) to reduce resistance.

Aminoglycosides have a synergistic effect when combined with this group of drugs.

Side-Effects of Penicillins

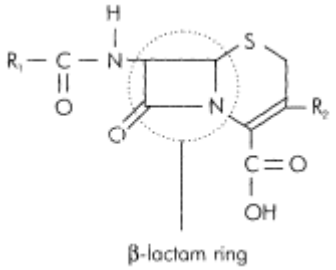
• Hypersensitivitythis is rare and ranges from rash to anaphylaxis, which may be fatal. True penicillin allergy results in hypersensitivity to all penicillins.

• Encephalopathymay result from very high doses or normal doses in renal impairment.

• Gutdiarrhoea is common during oral therapy.

• Miscellaneousampicillin may produce an erythematous rash during an episode of infectious mononucleosis.

2
Cephalosporins



Uses

The cephalosporins are broad-spectrum antimicrobials, all with a similar range of activity although certain agents have particular activity against specific bacteria.

Mechanism of Action

They contain a b-lactam ring structure and are bactericidal by combining with the transpeptidase used to cross link bacterial cell wall peptidoglycan. The cephalosporin b-lactam ring is more stable than that in the penicillins and so is less susceptible to b-lactamase.

• *First-generation (cephalexin, cephradine, cephadroxil)*

These are active orally and have essentially been replaced by the second-generation cephalosporins. Cephadroxil has a longer duration of action than other cephalosporins but has poor activity against *H. influenzae.* It is used in urinary tract infections when resistant organisms preclude other first line agents.

• *Second-generation (cefuroxime, ceflacor)*

These drugs are more resistant to b-lactamase and have a greater activity against *H. influenzae* and *Neisseria gonorrhoea.* Ceflacor may be administered orally but has been associated with prolonged skin reactions especially in children.

• *Third-generation (cefotaxime, ceftazidime, ceftriaxone)*

These drugs have improved activity against certain Gram-negative bacteria. However, their activity against Gram-positive bacteria is less than the second-generation agents. Their broad spectrum of activity may encourage superinfection with resistant bacteria or fungi. Ceftazidime has good activity against *Pseudomonas.* Ceftriaxone has a long duration of action due to its long half-life that allows once daily administration.

Side-Effects of Cephalosporins

• Hypersensitivitycephalosporin hypersensitivity occurs less frequently than penicillin hypersensitivity. Between 5 and 10% of patients with penicillin hypersensitivity will also be hypersensitive to cephalosporins.

Kinetics

The kinetics of the cephalosporins are similar to the penicillins, with variable intestinal absorption and active renal elimination which is blocked by probenecid. They should be used with caution in renal failure.

3
Other b-*Lactams*

Impienem

This bactericidal carbapenem has a very broad spectrum of activity including many aerobic and anaerobic organisms. It is also resistant to b-lactamase producing organisms.

Kinetics

Imipenem is partially metabolized by renal dehydropeptidase-I and is, therefore, presented in combination with cilastatin (itself devoid of antimicrobial activity) which inhibits this metabolism and increases plasma concentration. It is mainly excreted unchanged in the urine and will accumulate in renal failure.

Side-Effects

• Imipenem is generally well tolerated but may cause vomiting and diarrhoea (including pseudomembranous colitis), a positive Coombs' test, allergic reactions and convulsions (usually in cases of relative overdose, i.e. associated with renal insufficiency)

Meropenem

Meropenem is similar to imipenem but is not metabolized by renal dehydropeptidase-I and, therefore, may be administered without cilastatin.

4
Tetracyclines:
Tetracycline and Doxycycline

Uses

These are broad-spectrum antibiotics that are used less frequently today due to increasing patterns of resistance. However, due to their good penetration of macrophages they are still used in the treatment of intracellular infection (e.g. *Chlamydia,* rickettsia (Q fever) and *Mycoplasma*).

Mechanism of Action

They are bacteriostatic and inhibit bacterial protein synthesis by binding to the bacterial 30S ribosomal subunit. This prevents tRNA binding to the ribosome so that the addition of further amino acids to the peptide chain is blocked.

Side-Effects

• Dentalowing to deposition in growing bone and teeth (causing staining and dental hypoplasia), tetracyclines are contraindicated in children under 12 years of age and in the pregnant or breast feeding woman.

• Renalmany tetracyclines (but not doxycycline or minocycline) exacerbate renal failure.

Kinetics

They are usually given orally but absorption is reduced by iron preparations, calcium and magnesium salts. They are subject to minimal metabolism and are mainly excreted in the urine though also in faeces.

5
Aminoglycosides (Gentamicin, Netilmicin, Amikacin, Neomycin, Streptomycin)

Uses

Aminoglycosides are effective against some Gram-positive and many Gram-negative organisms. Their actions are synergistic with penicillins and vancomycin. Streptomycin is active against *Mycobacterium tuberculosis* and is only used in this setting. Neomycin is too toxic for systemic administration and is only used orally for bowel sterilization before surgery because it is not absorbed.

Mechanism of Action

Aminoglycosides are bactericidal and block protein synthesis in a similar manner to tetracyclines. However, they also cause the misreading of mRNA so that nonfunctional proteins are synthesized.

Other Effects

• Ototoxicity (vestibular and or auditory dysfunction) and nephrotoxicity (a form of acute tubular necrosis) are the most serious side-effects and

are seen when drug accumulates due to excessive dose or reduced excretion. Loop diuretics exacerbate these side-effects.

• Muscle weaknessaminoglycosides decrease the prejunctional release of acetylcholine and reduce postjunctional sensitivity to acetylcholine and, therefore, potentiate non-depolarizing muscle relaxants. Intravenous calcium may reverse this effect. Their use is cautioned in myasthenia gravis.

Kinetics

Owing to their low lipid solubility aminoglycosides are not absorbed from the gut and must, therefore, be given parenterally. They are not metabolized and are excreted unchanged in the urine by filtration. Accumulation occurs in renal failure. Owing to their narrow therapeutic index blood assays should be checked before and 1 hour after a dose to determine the most appropriate dose and the adequacy of its clearance.

6
Macrolides (Erythromycin, Azithromycin, Clarithromycin)

Uses

This group of drugs has a range of activity similar to penicillin and may be used as alternative therapy in penicillin allergy. However, they have specific activity against *Mycoplasma* and *Legionella* for which they are indicated.

Mechanism of Action

They inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit and inhibiting translocation.

Side-Effects

• Gutnausea, vomiting and diarrhoea occur especially following intravenous injection due to a prokinetic effect. Various hepatic dysfunction has been reported but is usually reversible.

• Cardiovasculara prolonged QT interval is associated with erythromycin and clarithromycin and may precipitate ventricular tachycardia or torsades de pointes especially when taken with terfenadine or cisapride.

• Interactionsthe actions of theophylline, warfarin and digoxin may all be potentiated when given with macrolides. Erythromycin should be avoided in porphyria.

Kinetics

This group of bacteriostatic antimicrobials is usually given orally but may also be given parenterally. All are metabolized and excreted mainly via the liver. Urinary excretion accounts for only a fraction of their clearance.

Erythromycin inhibits hepatic cytochrome P450 (3A), which is responsible for the metabolism of alfentanil and midazolam so that concurrent use leads to raised serum levels of these drugs.

7
4-Quinolones (Nalidixic Acid, Norfloxacin, Ciprofloxacin)

Uses

Nalidixic acid is only used for urinary tract infections. Ciprofloxacin is active against a wide range of Gram-negative and some Gram-positive bacteria and has excellent tissue penetration.

Mechanism of Action

The 4-quinolones are bactericidal by inhibiting DNA gyrase, which leads to cell death via uncoiling of DNA supercoils.

Side-Effects of Ciprofloxacin

• Central nervous systemit should be used with caution in epileptic patients and it may cause restlessness, confusion and seizures.

• Gutnausea, vomiting and abdominal pain can all occur.

• Haematologicalhaemolytic reactions can occur in patients with defects of glucose 6-phosphate dehydrogenase.

• Interactionsthe half-life of concurrently administered theophylline is increased. It is recommended that where concurrent administration is necessary theophylline levels are measured.

• Allergic reactions and transiently altered liver function have been reported.

Kinetics

Ciprofloxacin is well absorbed from the gut although this is reduced in the presence of magnesium, calcium or iron salts and sucralfate. It undergoes limited metabolism to active metabolites, and excretion is via urine and faeces mainly in the unchanged form. Dose reduction is only required in severe renal impairment.

8
Others

Sodium Fusidate

Sodium fusidate is a narrow-spectrum antibiotic used only for penicillin-resistant staphylococci, especially those causing osteomyelitis. Its tissue penetration is excellent. In severe infection it should be given with another anti-staphylococcal agent to prevent the emergence of resistant strains. However, resistance to sodium fusidate remains low.

It may be given orally or intravenously. It displaces bilirubin from albumin and may alter liver function tests especially during prolonged treatment. Excretion is mainly in the bile and it does not, therefore, accumulate in renal impairment.

Side-Effects

- Reversible jaundice
- Thrombophlebitis

Vancomycin

Vancomycin is a complex glycopeptide containing vancosamine and several amino acid moieties.

Uses

Vancomycin is active against most Gram-positive bacteria but is not used as a firstline agent due to its potential for toxicity. It is used, however, to treat methacillin-resistant *Staphylococcus aureus* (MRSA), and as prophylaxis in patients at high risk of endocarditis who are allergic to penicillin. However, there have recently been isolated cases of vancomycin-resistant *S. aureus.*

Mechanism of Action

Vancomycin is bactericidal and prevents peptidoglycan formation in the bacterial cell wall by inhibition of the enzyme glycopeptide synthetase.

Side-Effects

- Renalnephrotoxicity is rare but is usually seen with concurrent administration of aminoglycosides or with pre-existing renal impairment. It usually resolves on withdrawal of vancomycin.
- Ototoxicityvery rare and usually associated with pre-existing hearing loss, renal impairment or concomitant treatment with another ototoxic drug.
- Phlebitisthe intravenous preparation should be diluted when given peripherally.
- Histamine releaseif administered too rapidly histamine release may cause hypotension, tachycardia and a widespread rash (known as the 'red man syndrome').
- Haematologicalneutropenia and thrombocytopenia are rare and reversible.

Kinetics

It is not absorbed from healthy intestine so is used orally for antibiotic associated pseudomembranous colitis due to *Clostridium difficile.* Following intravenous

administration there is marked variability in the kinetics between individuals with the elimination half-life varying between 3 and 13 hours. Plasma protein binding is quoted between 10 and 80%, the variation is probably due to methodological differences.

Systemic infections require intravenous administration that should be monitored with blood assays. It is eliminated essentially in the urine as unchanged drug.

Teicoplanin

Teicoplanin is a similar antibiotic to vancomycin but with a longer duration of action allowing once daily administration. It is also bactericidal and useful against serious Gram-positive infections. It is excreted unchanged in the urine.

Metronidazole

Metronidazole is a synthetic imidazole derivative. It diffuses into bacteria where the nitro-group is reduced causing the release of reactive intermediates that interfere with DNA synthesis and function. It is bactericidal against most anaerobic bacteria and certain protozoa. It is well absorbed from the gut, partially metabolized in the liver and excreted in the urine, mainly unchanged.

Side-Effects

- Gutit may produce mild gastrointestinal upset, and a metallic taste.
- Interactionit produces a disulfiram-like reaction with alcohol resulting in an acute confusional state.

Selective Decontamination of the Digestive Tract (SDD)

The SDD refers to an antibiotic regime that aims to reduce the incidence of nosocomial pneumonia and multiple organ dysfunction syndrome in critically ill patients by selective eradication of pathogenic gut microorganisms, in particular Gram-negative organisms. The anaerobic gut flora are important to prevent overgrowth of Gram-negative enteric bacilli; therefore, metronidazole is specifically contraindicated in those patients on the SDD regime. Many antibiotic regimes have been used. The original regime is shown in Table 21.1.

There is some evidence that SDD reduces the incidence of Gram-negative nosocomial pneumonia and mortality in critically ill trauma patients. However, it has been impossible to reproduce these results when used in a heterogeneous group of intensive care patients. Despite this, those patients with burns or fulminant hepatic failure may do better if treated with an SDD regime.

There has been concern that SDD may lead to resistant strains of bacteria, but this appears to be unjustified at present.

Table 21.1: An SDD regime.

Route of administration	Drug
Nasogastric	tobramycin, polymyxin, amphotericin B
Intravenous	cefotaxime
Topical paste to oropharynx	tobramycin, polymyxin, amphotericin B

Antifungal Drugs

1
Polyenes (Amphotericin)

Uses

Amphotericin is a wide spectrum antifungal used in the treatment of serious systemic infections. Its spectrum of activity includes *Aspergillus, Candida* and *Cryptococcus.*

Mechanism of Action

Amphotericin reacts with ergosterol in the fungal cell membrane, creating pores through which cell contents are lost. It reacts less well with cholesterol and is, therefore, less toxic to human cells.

Side-Effects

• Renalrenal impairment is only reversible if treatment is stopped early. Amphotericin formulated in liposomes is less nephrotoxic but considerably more expensive.

• Miscellaneousit may cause any of the following: gastrointestinal upsets, blood dyscrasias, febrile reactions, muscle pains, visual and hearing disturbances, convulsions, anaphylaxis and altered liver function tests.

Kinetics

Gastrointestinal absorption is poor so it is given intravenously. It is highly plasma protein-bound and penetrates poorly into tissues. It appears to be metabolized by the liver and excreted in the urine.

Nystatin is mainly used for non-systemic infections due to *Candida albicans.* It is too toxic to give parenterally and not absorbed from the gut.

2
Imidazoles (Clotrimazole, Ketoconazole, Miconazole)

The imidazoles are active against a wide range of fungi and yeasts. They are all poorly absorbed from the gut except ketoconazole, which may be given orally. Miconazole is used intravenously in patients with systemic infection who are

unable to tolerate amphotericin. Ketoconazole may cause hepatitis especially when administered for more than 14 days.

3
Triazoles (Fluclonazole, Itraconazole)

Fluclonazole may be given orally or intravenously and has a wide range of activity (but not against *Aspergillus*). Itraconazole is absorbed orally and is active against *Aspergillus.*

The imidazoles and triazoles should not be given with cisapride because they inhibit its metabolism. If serum levels of cisapride rise the QT interval may be prolonged, which in turn may precipitate serious ventricular arrhythmias.

Antiviral Drugs

Viruses utilize the biochemical components of their host cell and it is, therefore, difficult to prevent viral replication without causing damage to the host cell.

Acyclovir

Uses

It is used to treat infection due to *Herpes simplex* and *Varicella zoster.*

Mechanism of Action

Acyclovir inhibits nucleic acid synthesis. Cells infected with *H. simplex* or *V. zoster* contain a thymidine kinase (from viral code) that converts acyclovir to a monophosphate and then to an active triphosphate which inhibits viral DNA polymerase and synthesis. The thymidine kinase present in uninfected cells has only a low affinity for acyclovir so that only very small amounts of acyclovir triphosphate are produced. This variable affinity forms the basis of its selectivity.

While it is useful against these viruses it does not eradicate them and is only effective if given at the start of an infection.

Side-Effects

- Renalrapid intravenous administration may precipitate renal impairment and the dose should be reduced in renal failure.
- Thrombophlebitisit is highly irritant to veins and may cause ulcers when extravasated.
- Central nervous systemtremors, confusion, seizures and coma during rapid intravenous administration are recognized.

Kinetics

Intestinal absorption is erratic and the oral bioavailability is low (approximately 25%). It is partially metabolized to inactive compounds and undergoes active tubular excretion into the urine.

Zidovudine

Uses

Zidovudine is used to treat the human immunodeficiency virus (HIV) in combination with other antiviral agents.

Mechanism of Action

Zidovudine is a nucleoside reverse transcriptase inhibitor (or nucleoside analogue). Once inside cells it is converted by kinases to zidovudine triphosphate, which is the active compound. This is incorporated into proviral DNA, which prevents further DNA polymerization. Its affinity for HIV reverse transcriptase is 100 times greater than for host DNA polymerase.

Side-Effects

- Haematologicalanaemia and neutropenia.
- Gutgastrointestinal upset and anorexia. Deranged LFTs and lactic acidosis with steatorrhea.
- Miscellaneousheadache, myalgia, parasthesia and pigmentation of nail beds and oral mucosa.

Kinetics

Zidovudine is given orally or intravenously and conjugated in the liver. Up to 80% is excreted in the urine as the glucuronide.

Table 21.2: Antibacterial prophylaxis.(*Special risk* = prosthetic valve or previous endocarditis; *recent pencillin* = within the previous month)

Prevention of:	Type of surgery	Type of anaesthesia	Patient details	Options for prophylaxis (NB adult doses)
Endocarditis in patients with:	Dental	Local or none	No recent penicillin	• Amoxycillin (3 g p.o.) 1 h pre-op
• Valve lesion or prosthetic valve,			Penicillin allergic or recent penicillin	• Clindamycin (600 mg p.o.) 1 h pre-op
• septal defect, • patent ductus			Previous endocarditis	• Amoxycillin (1 g i.v.) & gentamicin (120 mg i.v.), then amoxycillin (500 mg p.o.) 6 h later
		General	*No special risk*	• Amoxycillin (1 g i.v.) at induction, then amoxycillin (500 mg p.o.) 6 h later • amoxycillin (3 g p.o.) 4 h pre-op, then amoxycillin (3 g p.o.) asap post-op

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Prevention of:	Type of surgery	Type of anaesthesia	Patient details	Options for prophylaxis (NB adult doses)
				• Amoxycillin (3 g p.o.) and probenecid (1 g p.o.) 4 h pre-op
			Special risk	• Amoxycillin (1 g i.v.) and gentamicin (120 mg i.v.) at induction, then amoxycillin (500 mg p.o.) 6 h later
			Penicillin allergic or recent penicillin	• Vancomycin (1 g i.v.) pre-op and gentamicin (120 mg i.v.) at induction
				• Teicoplanin (400 mg i.v.) and gentamicin (120 mg i.v.) at induction
				• Clindamycin (300 mg i.v.) at induction, then Clindamycin (150 mg i.v. or p.o.) 6 h later
	Upper respiratory tract			• As for Dental
	Genito-urinary			• As for Dental/GA/ Special risk (except clindamycin not used). NB if urine infected, ensure prophylaxis covers infecting organism
	Obstetrics, Gynaecology and GI procedures			• As for Genito-urinary (but prophylaxis only required for those at *special risk*)
Meningococcal meningitis				• Rifampicin (600 mg p.o.) bd for 2 days • Ciprofloxacin (500 mg p.o.) single dose • Ceftriaxone (250 mg i.m.) single dose
Pneumococcal infection (in asplenia or sickle cell disease)				• Penicillin V (500 mg bd)
Infection in abdominal surgery			Upper GI Surgery	• Gentamicin • A cephalosporin 2 h pre-op
			Lower GI Surgery	• Gentamicin and metronidazole • Cefuroxime and metronidazole
			Hysterectomy	• Metronidazole

Table 21.3: Summary of some antibacterial drugs.

Drug	Use	Notes
Benzylpenicillin	streptococcal, pneumococcal, gonococcal and meningococcal infection. Anthrax, diphtheria, Gas-gangrene, syphilis, tetanus, yaws	established resistance to pneumococcal, gonococcal and meningococcal infection. No longer drug of first choice in meningococcal meningitis
Phenoxymethylpenicillin	mild streptococcal infection. Prophylaxis against pneumococcal infection following splenectomy or during sickle disease	oral preparation only, so not to be used in serious infection
Flucloxacillin (isoxazyl penicillins)	*Staphylococcus*	may cause cholestatic jaundice
Amoxycillin (aminopenicillins)	*Streptococcus, H. influenzae,* gonorrhoea and many coliforms	resistance from 90% of *Staphylococci*, 50% *E. coli* and 15% *H. influenzae* reduced when combined with clavulinic acid. May cause cholestatic jaundice
Azlocillin, piperacillin (ureidopenicillins)	pseudomonal sepsis	combined with b-lactamases to reduce resistance. Synergy with aminoglycosides
Cefadroxil (first-generation cephalosporin)	*Staphylococcus, Streptococcus* (not enterococci), *Salmonella, E. coli, Klebsiella, Proteus* and some activity against *Haemophilus* and *Neisseria gonorrhoea*	oral preparation
Cefuroxime (second-generation cephalosporin)	similar to first-generation cephalosporins but with improved action against *Haemophilus* and *Neisseria gonorrhoea*	resistant to inactivation by b-lactamases
Cefotaxime (third-generation cephalosporin)	similar to second-generation cephalosporins but with improved action against *Pseudomonas.* It is used in meningitis caused by sensitive organisms as it penetrates the CNS well	less active than cefuroxime against Gram-positive bacteria

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Drug	Use	Notes
Imipenem	Gram-negative aerobes (*E. coli, Proteus, Serratia, Klebsiella, Enterobacter, Campylobacter, Salmonella, Pseudomonas, Haemophilus, Neisseria*); Gram-positive aerobes (*Streptococcus* and *Staphylococcus*); Gram-negative anaerobes (*Bacteroides* and *Fusobacterium*); Gram-positive anaerobes (*Actinomyces, Clostridium*)	not for CNS infection. Some MRSA not sensitive. Synergy with aminoglycosides against *Pseudomonas*
Tetracycline	*Chlamydia,* rickettsia, *Mycoplasma, Borrelia burgdorferi* (Lyme disease), *Haemophilus*	intestinal chelation with Ca2+ and Mg2+ reduces absorption. May discolour teeth in children
Gentamicin	E. coli, Klebsiella, Proteus, Pseudomonas, Staphylococcus (M. tuberculosis)	blood assays required. Oto- and nephrotoxicity. *Streptococcus* and anaerobes are resistant
Erythromycin	*Staphylococcus, Streptococcus, Haemophilus, Mycoplasma, Legionella, Branhamella, Treponema, Neisseria, Bacteroides, Corynebacterium*	highly irritant to peripheral veins. Potentially serious drug interactions
Vancomycin	*Staphylococci,* a- and b-haemolytic *Streptococci,* group D *Streptococci* and *Clostridia*	used in MRSA. Potential for serious toxicity. Blood assays required
Ciprofloxacin	Gram-negative (*Salmonella, Shigella, Campylobacter, Neisseria* and *Pseudomonas*). It has moderate activity against Gram-positive bacteria (*Streptococcus* pneomoniae and *Strep. faecalis.*) but Staphylococci are usually resistant	excellent tissue penetration
Metronidazle	anaerobes and certain protozoa (*Entamoeba, Giardia, Trichomonas*)	interacts with alcohol

22
Drugs Affecting Coagulation

- Anti-platelet drugs
- Heparins and protamine
- Oral anticoagulants
- Drugs affecting the fibrinolytic system

Physiology

The coagulation of blood is complicated. It has three elements: platelets, the coagulation cascade and fibrinolysis. The first two are involved in preventing haemorrhage by thrombus formation, while fibrinolysis is an essential limiting mechanism.

Thrombus formation is initially dependent on platelet adhesion, which is triggered by exposure to subendothelial connective tissue. The von Willebrand factor, which is part of the main fraction of factor VIII, is essential in this process. Subsequent platelet aggregation and vasoconstriction is enhanced by the release of thromboxane A2 (TXA2) from platelets. Adjacent undamaged vascular endothelium produces prostacyclin (PGI2), which inhibits aggregation and helps to localize the platelet plug to the damaged area. The localized primary platelet plug is then enmeshed by fibrin converting it to a stable haemostatic plug.

The coagulation cascade is formed by an intrinsic and extrinsic pathway, which converge to activate factor X and the final common pathway (Figure 22.1). The intrinsic pathway is triggered by the exposure of collagen, thereby activating factor XII, while the extrinsic pathway is triggered by leakage of tissue factors, activating factor VII.

Venous thrombus consists mainly of a fibrin web enmeshed with platelets and red cells. Arterial thrombus relies more on platelets and less on the fibrin mesh.

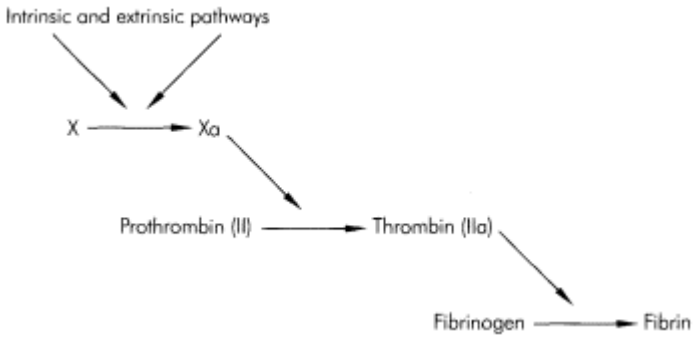

Figure 22.1:
Final common pathway of the coagulation cascade.

A crucial part of this process is its limitation to the initial site of injury. Circulating inhibitors, of which anti-thrombin III is the most potent, perform this function. In addition, a fibrinolytic system is activated by tissue damage, converting plasminogen to plasmin, which converts fibrin into soluble degradation products.

Anti-Platelet Drugs

Aspirin

Uses

Aspirin reduces the risk of unstable angina progressing to acute myocardial infarction (MI) and reduces the mortality following acute MI. The risk of stroke is also reduced for patients with transient ischaemic attacks.

Mechanism of Action

Aspirin acts by irreversible inhibition of cyclo-oxygenase (by acetylation) within the platelet resulting in reduced production of TXA2. This may be achieved with only 75 mg daily. Its effects and kinetics are discussed in Chapter 9.

Dipyridamole

Uses

Dipyridamole has been used with limited success in conjunction with warfarin to prevent thrombus formation on prosthetic valves. It is a potent coronary artery vasodilator and may be used in conjunction with thallium201 during myocardial imaging.

Mechanism of Action

Dipyridamole interferes with platelet aggregation. It reversibly inhibits platelet phosphodiesterase activity resulting in increased cAMP levels, reduced intracellular Ca2+ and inhibition of phospholipase activity. It also inhibits adenosine uptake into platelets which reduces platelet aggregation.

Dextran 40 and Dextran 70

These are polysaccharides that contain chains of glucose. They are produced by the fermentation of sucrose by the bacterium *Leuconostoc mesenteroides.*

Uses

They are used as prophylaxis against peri-operative venous thrombosis and as plasma volume expanders.

Mechanism of Action

Their anticoagulant activity appears to depend on reducing platelet adhesiveness and a specific inhibitory effect on the von Willebrand factor. They also reduce red cell aggregation and provide a protective coat over vascular endothelium and erythrocytes. The dilution of clotting factors and volume expansion also improves microcirculatory flow.

Other Effects

These include fluid overload, allergic reactions and anaphylaxis. Dextran 70 can impair cross matching by rouleaux formation. Renal failure is a rare complication.

Epoprostenol (ProstacyclinPGI2)

This is a naturally occurring prostaglandin.

Uses

Epoprostenol is used to facilitate haemofiltration by continuous infusion into the extracorporeal circuit.

Mechanism of Action

Epoprostenol causes inhibition of platelet adhesion and aggregation by stimulating adenylate cyclase. The ensuing rise in cAMP reduces intracellular Ca2+, effecting the change. It may also have a fibrinolytic effect. The recommended dose range is 212 ng.kg1.min1

Side-Effects

These relate to its vasodilator properties (hypotension, tachycardia, facial flushing and headache).

Heparins and Protamine

Unfractionated Heparin

Heparin is an anionic, mucopolysaccharide, organic acid containing many sulphate residues. It occurs naturally in the liver and mast cell granules and has a variable molecular weight (500025 000 Da).

Uses

Unfractionated heparin is used by continuous intravenous infusion to treat deep vein thrombosis (DVT), pulmonary embolus (PE), unstable angina and in critical peripheral arterial occlusion. Subcutaneous administration helps prevent venous thrombosis peri-operatively and in the critically ill. It is also used in the priming of extracorporeal circuits. There has been limited use in disseminated intravascular coagulation (DIC).

Mechanism of Action

When anti-thrombin III combines with thrombin an inactive 'anti-thrombinthrombin' complex is formed (Figure 22.2). The rate of formation of this complex is increased 1000-fold by heparin. At low concentrations factor Xa is inhibited, while factors IXa, XIa and XIIa are progressively inhibited as heparin concentrations rise. Platelet aggregation becomes inhibited at high concentrations and plasma triglyceride levels are lowered due to the release of a lipoprotein lipase from tissues, which reduces plasma turbidity.

Side-Effects

- Haemorrhagethis is the most common side-effect and is due to a relative overdose.

- Thrombocytopeniamild thrombocytopenia seen after initial administration may be due to an anaphylactoid type reaction. Severe thrombocytopenia, which occurs later and is often associated with heparin resistance and serious thrombotic events carrying a high mortality, is thought to be due a type II hypersensitivity reaction.

- Cardiovascularhypotension may follow rapid intravenous administration of a large dose.

- Miscellaneousosteoporosis, due to complexing of mineral substance from bone, and alopecia have been reported.

Kinetics

As the potency of commercial preparations varies unfractionated heparin is presented as units.ml1 rather than mg.ml1. It is ineffective orally and may only be given subcutaneously or intravenously. It has a low lipid solubility and does not cross the bloodbrain barrier or placenta. Owing to its negative charge it is highly

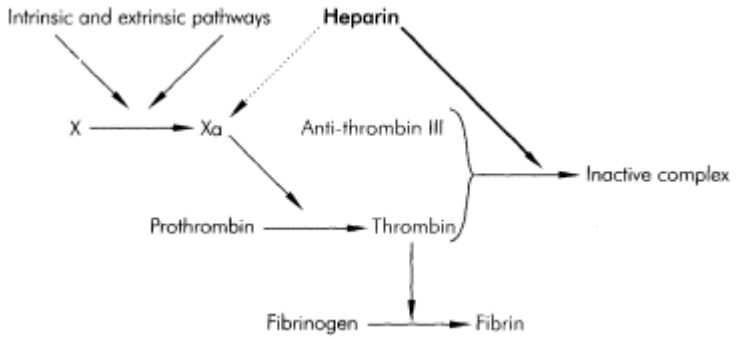

Figure 22.2:
Actions of heparin. Heparin augments (→) the formation of the inactive 'anti-thrombinthrombin' complex, while inhibiting (→) factors Xa, IXa, XIa and XIIa.

bound in plasma to anti-thrombin III, albumin, proteases and fibrinogen. It is metabolized by hepatic heparinase and the products are excreted in the urine. During hypothermia (e.g. cardiopulmonary bypass) clearance is reduced. Its effects are reversed by protamine.

Low Molecular Weight Heparins (LMWHs) (Enoxaparin, Dalteparin, Tinzaparin)

These drugs are derived from the depolymerization of heparin by either chemical or enzymatic degradation. Their molecular weights vary from 2000 to 8000 Da.

Mechanism of Action

Compared with unfractionated heparin, LMWHs are more effective at inhibiting factor Xa and less effective at promoting the formation of the inactive 'anti-thrombinthrombin' complex.

Uses

LMWHs have proven benefit over unfractionated heparin in reducing the incidence of fatal PE after major orthopaedic surgery.

Other advantages include:

- Single daily dose, due to a longer half-life
- Reduced affinity for von Willebrand factor
- Less effect on platelets
- Reduced risk of heparin induced thrombocytopenia
- Reduced need for monitoring

Protamine is not fully effective in reversing the effects of LMWH.

Monitoring Heparin Therapy

The activated partial thromboplastin time (APTT) measures the intrinsic system factors (VIII, IX, XI and XII) in addition to the factors common to both systems. Phospholipid, a surface activator (e.g. kaolin) and Ca2+ are added to citrated blood. The clotting time varies between laboratories but is about 2835 seconds.

Monitoring LMWH is difficult as its main effects are inhibiting factor Xa, so the APTT is not altered.

Protamine

Protamine is a basic protein prepared from fish sperm. Its positive charge enables it to neutralize the anticoagulant effects of heparin by the formation of an inactive complex that is cleared by the reticulo-endothelial system. It is also used in the formulation of certain insulins.

It is given intravenously, 1 mg reversing 100 i.u. heparin.

Side-Effects

- Cardiovascularhypotension (due to histamine release), pulmonary hypertension (complement activation and thromboxane release), dyspnoea, bradycardia and flushing follow rapid intravenous administration.

- Allergic reactionspatients having previously received insulin containing protamine, and those allergic to fish may be at increased risk of allergic reactions.

- Anticoagulationwhen given in excess it has some anticoagulant effects.

Oral Anticoagulants

Warfarin

Uses

Warfarin is a coumarin derivative and is used for the prophylaxis of systemic thrombo-embolism in patients with atrial fibrillation, rheumatic valve disease or prosthetic valves. It is also used in the prophylaxis and treatment of DVT and PE.

Mechanism of Action

Warfarin inhibits the synthesis of the vitamin K-dependent clotting factors: II (prothrombin), VII, IX and X. The precursors of these clotting factors are produced in the liver and are activated by g-carboxylation of their glutamic acid residues. This process is linked to the oxidation of reduced vitamin K. Warfarin acts by preventing the return of vitamin K to the reduced form (Figure 22.3).

Circulating factors will not be affected by the actions of warfarin, which therefore takes up to 72 hours to exert its full effect.

Side-Effects

- Haemorrhage

- Teratogenicitythis is more common and serious in the first trimester. During the third trimester it crosses the placenta and may result in foetal haemorrhage.

- Drug interactionsdrugs that impair other aspects of coagulation (NSAIDs and heparin) will potentiate the effects of warfarin. Competition for plasma binding sites (NSAIDs) and inhibition of metabolism (cimetidine, alcohol, allopurinol, erythromycin, ciprofloxacin, metronidazole and TCAs) lead to potentiation of warfarin's effects. Barbiturates, rifampicin and carbemazepine induce hepatic enzymes and antagonize the effects of warfarin. Cholestyramine interferes with the absorption of fat-soluble vitamins and thereby potentiates the action of warfarin. The effects of warfarin are rapidly reversed by fresh frozen plasma. Vitamin K (1 mg) will also reverse its effects but more slowly, while 10 mg vitamin K will prevent anticoagulation for a number of days. Spinal and epidural anaesthesia is contraindicated in patients anticoagulated with warfarin.

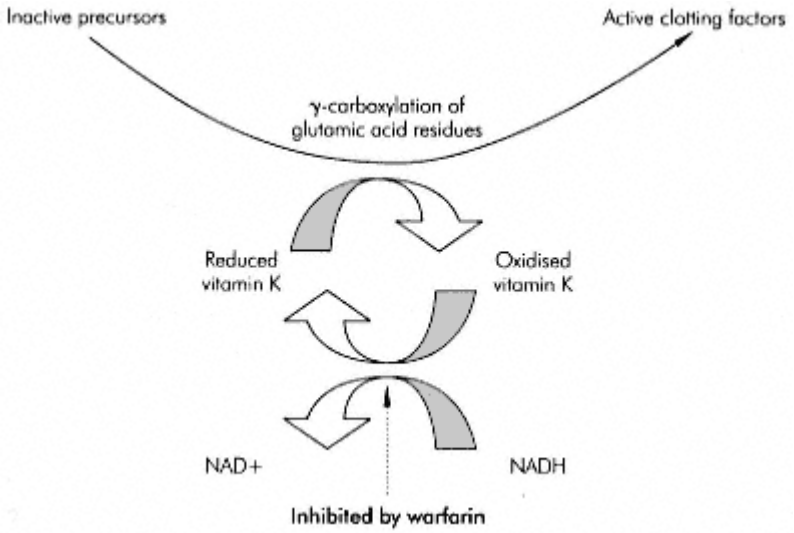

Figure 22.3:
Mechanism of action of warfarin.

Kinetics

Warfarin is completely absorbed from the gut and highly protein bound (> 95%). It undergoes complete hepatic metabolism by oxidation and reduction to products that are subsequently conjugated and excreted in the urine.

Monitoring Warfarin Therapy

Prothrombin time (PT) is a measure of the extrinsic system (VII) and factors common to both systems. Tissue thromboplastin (a brain extract) and Ca2+ are added to citrated plasma. Clotting normally takes place in 1014 seconds. The international normalized ratio (INR) is a ratio of the sample PT to a control international standard PT. Warfarin treatment should aim to increase the PT so that the INR is raised to between 2.0 and 4.5 depending on the clinical situation.

Drugs Affecting the Fibrinolytic System

Fibrinolytics:
Streptokinase

Streptokinase is an enzyme produced by group C b-haemolytic streptococci.

Uses

Streptokinase is used to dissolve clot in arterial (acute MI, occluded peripheral arteries and PE) and venous (DVT) vessels.

Mechanism of Action

Streptokinase activates the fibrinolytic system by forming a complex with plasminogen, which then facilitates the conversion of further plasminogen to active plasmin. Clot can then be lysed.

Side-Effects

- Haemorrhagestreptokinase is contraindicated in patients where a risk of serious bleeding outweighs any potential benefit of therapy (i.e. active internal bleeding, recent stroke, severe hypertension).

- Cardiovascularit may precipitate reperfusion arrhythmias and hypotension during treatment of acute MI.

- Allergic reactions may occur as it is very antigenic. Where high antibody titres are expected (5 days to 12 months from previous exposure to streptokinase) an alternative should be sought.

Kinetics

Streptokinase is administered intravenously as a loading dose followed by an infusion. The loading dose is sufficient to neutralize any antibodies that are often present from previous exposure to streptococcal infection. The streptokinaseantibody complex is cleared rapidly and the streptokinaseplasminogen complex is degraded to a number of smaller fragments during its action.

Alteplase (rt-PA, tissue type plasminogen activator) is a glycoprotein that becomes activated only when bound to fibrin, inducing the conversion of plasminogen to plasmin. Owing to its mode of activation, systemic fibrinolysis occurs to a lesser extent than with streptokinase.

Urokinase was originally extracted from human adult male urine but is now prepared from renal cell cultures. Recombinant DNA technology is currently used to produce pro-urokinase. It is not antigenic and is used in the lysis of clots in arteriovenous shunts and in hyphaema (anterior chamber haemorrhage with refractory thrombi).

Antifibrinolytics

Tranexamic acid competitively inhibits the conversion of plasminogen to active plasmin. It is used to control bleeding due to excessive fibrinolysis, which may be local (prostatectomy or surgical procedures in haemophiliacs) or systemic (following intravenous fibrinolytic therapy or DIC). It is excreted essentially (95%) unchanged in the urine.

Aprotinin is a polypeptide with 58 amino acids and has a molecular weight of 6512 Da. It is a naturally occurring proteolytic enzyme inhibitor acting on trypsin, plasmin and tissue kallikrein. It inhibits the fibrinolytic activity of the streptokinaseplasminogen complex. In addition it has been suggested that it preserves platelet function and decreases activation of the clotting cascade. It has been used for the treatment of haemorrhage due to hyperplasminaemia. It has also been used in patients at high risk of bleeding during and after cardiopulmonary bypass.

Side-Effects

- Hypersensitivity reactions including anaphylaxis.

- Coagulationit prolongs the activated clotting time (ACT) of heparinized blood so that heparin/protamine protocols will need alteration during treatment with aprotinin.

Kinetics

Aprotinin is metabolized and eliminated by the kidney.

23
Hypoglycaemic Agents

- Insulin
- Sulphonylureas
- Biguanides
- Acarbose

Insulin

Physiology

Human insulin is a polypeptide of 51 amino acids and is formed by the removal of a connecting or 'C' peptide (34 amino acids) from pro-insulin. It has A and B chains, which are joined by two disulphide bridges. A third disulphide bridge connects two regions of the A chain:

Pro-insulin → Insulin + C peptide

Glucose forms the most potent stimulus for insulin release. It enters the b-cells of the islets of Langerhans in the pancreas, resulting in an increase in ATP which closes K+ channels. This causes depolarization and Ca2+ influx through voltagesensitive Ca2+ channels, which triggers insulin release. By way of negative feedback the K+ channels are re-opened. In health there is a continuous basal insulin release which is supplemented by bursts when plasma glucose levels rise. Following its release it is carried in the portal circulation to the liver (its main target organ) where about one-half is extracted and broken down, as glucose is converted to glycogen.

Insulin binds to the a-subunit of the insulin receptor, which consist of two a- and two b-subunits that span the cell membrane. Once bound, the whole complex is internalized. The mechanism by which this complex produces its effects is unclear but the tyrosine kinase activity of the b-subunit appears important.

Insulin affects carbohydrate, fat and protein metabolism. It promotes hepatic (and extrahepatic) uptake of glucose and subsequently facilitates the actions of enzymes required to convert glucose into glycogen. Glycogenolysis is inhibited. Fat deposition is also increased by the promotion of hepatic fatty acid synthesis and subsequent storage as triglycerides. Lipolysis is inhibited. The storage of amino acids as proteins (anabolism) is promoted and catabolism inhibited.

Preparations

Insulin used to be extracted from porcine or beef pancreas but now is almost entirely produced by recombinant DNA technology using *E. coli*. Preparations are classified as short-, medium- or long-acting. In the UK the standard insulin concentration is 100 units.ml1.

• Short-actingthis is a simple solution of insulin which may be administered intravenously. Its duration of action is only 30 minutes.

• Medium- and long-actingwhen insulin is complexed with zinc or protamine, or produced as crystals rather than in its amorphous form, its absorption is prolonged. This extends its duration of action to 1635 hours.

Side-Effects

When calorie intake is insufficient hypoglycaemia will ensue. If untreated this will lead to coma and death. All insulins are immunogenic but despite this immunological resistance is rare. Beef insulin has three different amino acids from human insulin while pork insulin has only one; the latter is therefore less immunogenic. Localized lipodystrophy is also rare.

Sulphonylureas

Two generations of sulphonylureas exist and have slightly different characteristics:

• First generationchlorpropamide, tolbutamide, acetohexamide.

• Second generationglibenclamide, gliclazide, glipizide.

Uses

Sulphonylureas are used to control non-insulin dependent diabetes (NIDDM), but should not replace dietary control.

Mechanism of Action

In general these drugs work at the pancreas by displacing insulin from b-cells in the islets of Langerhans. For this reason they are ineffective in insulin-dependent diabetics who have no functioning b-cells. They may also induce b-cell hyperplasia, while reducing both glucagon secretion and hepatic insulinase activity. During long-term administration they also reduce peripheral resistance to insulin.

Kinetics

Sulphonylureas are all well absorbed from the gut and have oral bioavailabilities greater than 80%. Albumin binds these drugs extensively in the plasma. Chlorpropamide undergoes hepatic metabolism, but to a much lesser extent than the others. A significant fraction is excreted unchanged in the urine and in the presence of renal failure its half-life is prolonged. The other drugs in this class are extensively metabolized in the liver to inactive metabolites (with the exception of glibenclamide whose active metabolites are probably of little clinical significance), which are subsequently excreted in the urine. Cimetidine inhibits their metabolism and, therefore, potentiates their actions. Drugs that tend to increase blood sugar (thiazides, corticosteroids, phenothiazines) antagonize the effects of the sulphonylureas and make diabetic control harder.

The second-generation sulphonylureas bind to albumin by non-ionic forces in contrast with tolbutamide and chlorpropamide that bind by ionic forces. Thus, anionic drugs such as phenylbutazone, warfarin and salicylate do not displace second-generation drugs to such an extent and may be safer during concurrent drug therapy.

Other Effects

Side-effects are generally mild but sometimes include gastrointestinal disturbances and rashes.

• Chlorpropamideits long half-life and partial reliance on renal elimination results in a greater chance of hypoglycaemia, especially in the elderly. It may also cause facial flushing and vomiting following alcohol and rarely may enhance antidiuretic hormone secretion resulting in hyponatraemia. Photosensitivity may also occur.

• Tolbutamidethis drug has been associated with cholestatic jaundice, deranged liver function and blood dyscrasias.

Biguanides

Metformin

Metformin is the only currently available biguanide in the UK.

Mechanism of Action

This is thought to include delayed uptake of glucose from the gut, increased peripheral insulin sensitivity (increasing peripheral glucose utilization) and inhibition of hepatic and renal gluconeogenesis.

Other Effects

Gastrointestinal disturbances including diarrhoea sometimes occur but are generally mild. More significantly is its ability to precipitate severe lactic acidosis

especially if taken by alcohol abusers or in the presence of renal impairment. It also lowers plasma cholesterol, triglycerides and low-density lipoproteins.

Kinetics

Metformin is slowly absorbed from the gut with a bioavailability of 60%. It is not bound by plasma proteins and is excreted unchanged in the urine. Renal impairment significantly prolongs its actions.

Acarbose

Acarbose is a competitive inhibitor of intestinal a-glucosidase with a specific action on sucrase. Polysaccharides are therefore not metabolized into their absorbable monosaccharide form. This delay in intestinal glucose absorption reduces the postprandial hyperglycaemia normally seen in diabetics.

It is not absorbed significantly and has few other systemic effects. Owing to an increased carbohydrate load reaching the bacterial flora in the large bowel patients may experience borborygmi, flatulence and diarrhoea. Hepatic transaminases may be transiently raised.

Peri-Operative Care of the Diabetic Patient

A regional technique is often more appropriate as the patient will be able to eat and return to their normal drug regime more rapidly.

If a general anaesthetic is indicated the aim is to minimize the metabolic derangement by providing a balance of fluid, electrolytes, glucose and insulin. There is no single best way to achieve this and the approach chosen will reflect the type of diabetes, medication and proposed operation.

Diabetes Non-insulin-dependent diabetic (NIDDM).

*Medication*long-acting tablets.

Operation Minor.

Action Transfer to short-acting tablets 1 week before surgery. Omit tablets on morning of operation. First on list. Treat as non-diabetic if blood sugar < 7 mmol.l1. Restart tablets with first meal.

Diabetes NIDDM.

*Medication*Long-acting tablets.

Operation Major.

Action Treat as insulin-dependent diabetic (IDDM). Once eating convert to soluble insulin before meals and revert to tablets when total insulin requirement is < 20 i.u.day1.

Diabetes	IDDM.
Medication	Insulin.
Operation	Major or minor.
Action	Alberti regime or insulin sliding scale.

Alberti Regime

Infusion of 500 ml 10% dextrose with 10 i.u. actrapid and 10 mmol KCl starting at 100 ml.h1. Blood sugar and potassium are measured every 2 hours and if adjustments are required a new infusion is prepared.

Insulin Sliding Scale

An infusion of 10% dextrose at 100 ml.hl is given alongside an infusion of soluble insulin. The starting hourly insulin rate is calculated by dividing the total daily units by 24. Blood sugar is measured hourly and the insulin rate is adjusted accordingly.

24
Corticosteroids and Other Hormone Preparations

- Glucocorticoids
- Drugs used in thyroid disease
- Oral contraceptives

Glucocorticoids

The adrenal cortex releases two classes of steroidal hormones into the circulation:

- Glucocorticoids (from the zona fasciculata and zona reticularis)
- Mineralocorticoids (from the zona glomerulosa)

The main endogenous glucocorticoid in humans is hydrocortisone. Synthetic glucocorticoids include prednisolone, methylprednisolone, betamethasone, dexamethasone and triamcinolone. They have metabolic, anti-inflammatory and immunosuppressive effects.

Metabolic Effects

Glucocorticoids facilitate gluconeogenesis (i.e. synthesis of glucose from a noncarbohydrate source, e.g. protein). Glycogen deposition and glucose release from the liver are stimulated but the peripheral uptake of glucose is inhibited. Protein catabolism is stimulated and synthesis inhibited.

When exogenous glucocorticoid is given in high doses or for prolonged periods the altered metabolism causes unwanted effects. Increased protein catabolism leads to muscle weakness and wasting. The skin becomes thin leading to striae, and gastric mucosa becomes susceptible to ulceration. Dietary protein will not reverse these changes. Altered carbohydrate metabolism leads to hyperglycaemia and glycosuria. Diabetes may be provoked. Fat is redistributed from the extremities to the trunk, neck and face. Bone catabolism leads to osteoporosis.

Anti-Inflammatory Effects

Glucocorticoids reduce the production of tissue transudate and cell oedema in acute inflammation. Circulating polymorphs and macrophages are prevented from reaching inflamed tissue. The production of inflammatory mediators (prostaglandins, leukotrienes and platelet-activating factor) is suppressed by the stimulation of lipocortin, which inhibits phospholipase A2. Normally phospholipase A2 would facilitate the breakdown of membrane phospholipids to arachidonic acid, the precursor of inflammatory mediators, in particular prostaglandins.

These effects may reduce the patient's resistance to infection (latent tuberculosis may become reactivated), and the normal clinical features usually present may be absent until the infection is advanced.

Immunosuppressive Effects

Glucocorticoids depress macrophage function and reduce the number of circulating T-lymphocytes. The transport of lymphocytes and their production of anti-bodies are also reduced. Interleukin 1 and 2 production is inhibited which reduces lymphocyte proliferation.

Other Effects

• Adrenal suppressionduring long-term steroid therapy there is adrenal suppression due to negative feedback on corticotrophin-releasing hormone and adrenocorticotrophic hormone (ACTH) (Figure 24.1). The adrenal gland becomes atrophic and remains so for many months after treatment has stopped. As a result the adrenal cortex cannot produce sufficient glucocorticoid when exogenous glucocorticoid is withdrawn abruptly or during periods of stress, i.e. infection or surgery. If supplementary hydrocortisone is not administered in such patients peri-operatively, they are at risk of hypotension and possibly cardiovascular collapse (see below). Following major surgery intramuscular hydrocortisone 25 mg tds should be given initially, and reduced over the course of 5 days. Alternatively 25 mg hydrocortisone may be given at induction, followed by an infusion of 100 mg over 24 hours, which may be stopped after 24 or 48 hours.

Table 24.1: Anti-inflammatory potential of various steroids.

Drug	Relative anti-inflammatory potency	Equivalent anti-inflammatory dose (mg)
Hydrocortisone	1	100
Prednisolone	4	25
Methylprednisolone	5	20
Triamcinolone	5	20
Dexamethasone	25	4

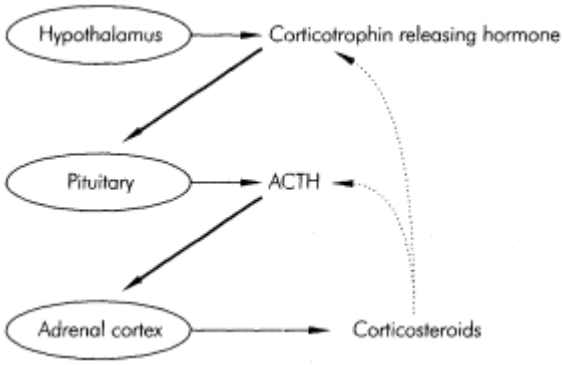

Figure 24.1:
Feedback loops affecting corticosteroid production. ——►, Stimulates; ·····►, inhibits

• Fluid retentionglucocorticoids have only weak mineralocorticoid activity. However, some do act on the distal renal tubule, leading to Na+ retention and K+ excretion. In very large doses water retention may cause oedema, hypertension and cardiac failure. Mineralocorticoid (sodium retaining) activity is greatest with hydrocortisone and cortisone, lesser with prednisolone, and least with methylprednisolone and dexamethasone.

• Vascular reactivityglucocorticoids have a 'permissive action' on vascular smooth muscle, allowing them to respond efficiently to circulating catecholamines. Therefore, glucocorticoid deficiency leads to an ineffective response by vascular smooth muscle to circulating catecholamines. In sepsis there may be an inappropriately reduced production of cortisol so that higher levels of inotropic support are required. This may be improved by the administration of intravenous hydrocortisone.

Other 'permissive actions' of glucocorticoids include the calorigenic effects of glucagon and catecholamines, and the lipolytic and bronchodilator effects of catecholamines.

Drugs Used in Thyroid Disease

Thyroid Replacement:
Thyroxine (T4)

The thyroid gland synthesizes triiodothyronine (T3) and thyroxine (T4) by combining iodine with tyrosine residues present in thyroglobulin. The release of T3

and T4 is controlled by the hypothalamic thyrotropin-releasing hormone (TRH) and thyrotropin (TSH), which are inhibited in the presence of T3 and T4 (Figure 24.2).

Uses

Replacement hormone is required to treat hypothyroidism, which may be due to thyroid, hypothalamic or pituitary disease. Synthetic T4 is the mainstay of oral replacement therapy but L-triiodothyronine (T3) may be given intravenously (550 µg according to response) in hypothyroid coma as it has a faster onset. T3 may also be given orally.

Mechanism of Action

Free T4 enters the cell via a carrier mechanism where most is converted to the more active T3. Their main intracellular targets are receptors on the mitochondria and cell nucleus to which they bind inducing a conformational change.

Effects

• Cardiovascularthyroid hormones exhibit positive inotropy and chronotropy. The cardiac output increases, while a reduced peripheral vascular resistance often leaves the mean arterial blood pressure unchanged. The increased myocardial oxygen demand may cause ischaemia in those with ischaemic heart disease.

• Respiratoryowing to an increased metabolic rate the minute volume increases.

• Central nervous systemthey act as central stimulants and may evoke tremor. They also act to inhibit TSH and TRH by negative feedback.

• MetabolicT3 affects growth, development, lipid metabolism, intestinal carbohydrate absorption and increases the dissociation of oxygen

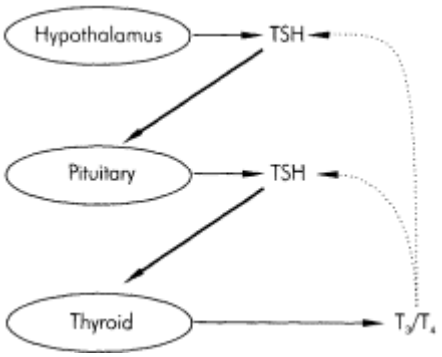

Figure 24.2:
Feedback loops affecting thyroid hormone production. ⟶, Stimulates; ⇢, inhibits

from haemoglobin by increasing red blood cell 2,3-diphosphoglycerol (2,3-DPG).

Kinetics

When administered enterally both T3 and T4 are well absorbed from the gut. Once in the plasma they are more than 99% bound to albumin and thyroxine-binding globulin. Some T4 is converted within the liver and kidneys to T3 or to the inactive reverse T3. Metabolism occurs in the liver and the conjugated products are excreted in bile. Up to 40% may be excreted unchanged in the urine.

Drugs Used in the Treatment of Hyperthyroidism:
Carbimazole

Carbimazole is a prodrug, being rapidly converted to methimazole in vivo.

Mechanism of Action

Carbimazole prevents the synthesis of new T3 and T4 by inhibiting the oxidation of iodide to iodine, and by inhibiting thyroid peroxidase, which is responsible for iodotyrosine synthesis and the coupling of iodotyrosines. Stored T3 and T4 is unaffected and so treatment with carbimazole requires weeks before the patient becomes euthyroid.

Side-Effects

These include rashes, arthralgia and pruritus. Agranulocytosis occurs rarely and may be heralded by a sore throat. It crosses the placenta and may cause foetal hypothyroidism; however, it is not contraindicated during breast feeding as only tiny amounts enter the breast milk.

Kinetics

Carbimazole is well absorbed from the gut and completely converted to methimazole during its passage through the liver. It increases the vascularity of and is metabolized within the thyroid gland. It is minimally plasma protein-bound.

Propylthiouracil

This oral preparation blocks the iodination of tyrosine and partially blocks the peripheral conversion of T4 to T3. There is no parenteral formulation and it is reserved for those patients intolerant of carbimazole. It has a slightly higher incidence of agranulocytosis.

Propranolol

Propranolol is a b-blocker with negative inotropic and chronotropic activity. It will help control the sympathetic effects of a thyrotoxic crisis. However, it also blocks the peripheral conversion of T4 to T3 and blocks hypersensitivity to the actions of catecholamines. It is relatively contraindicated for patients with heart failure or reversible airflow limitation. Guanethidine may be considered as an alternative in these cases.

Iodides

Iodide has been given as potassium iodide orally, sodium iodide intravenously and iodide containing radiographic contrast dyes. It is concentrated in the follicular cells where peroxidases oxidize it to iodine, which is then combined with tyrosine residues.

Iodide is required for normal thyroid function and when levels are too low or too high thyroid function becomes abnormal. Large doses cause inhibition of iodide binding and hence reduced hormone production. This effect is greatest when iodide transport is increased, i.e. in thyrotoxicosis. Iodide also reduces the effect of TSH on the thyroid gland and inhibits proteolysis of thyroglobulin. Thyroid vascularity is decreased which is useful pre-operatively, but iodide is not used for prolonged periods as its actions tend to diminish with time.

Lithium may be considered in those with iodide sensitivity.

Oral Contraceptives

The oral contraceptive pill (OCP) takes two forms: a combined oestrogen/progesterone preparation and a progesterone only preparation. The former is taken for 21 consecutive days followed by a 7 day break, while the latter is taken continuously.

Mechanism of Action

The combined preparation inhibits ovulation by suppressing gonadotrophin-releasing hormone and inhibiting gonadotrophin secretion. The progesterone only pill prevents ovulation in only 25% of women and appears to work by producing an unfavourable endometrium for implantation.

Side-Effects

• Majorthese include cholestatic jaundice and an increased incidence of thrombo-embolic disease. The following are considered a contraindication for the combined OCP: a history of thrombo-embolism, obesity, smoking, hypertension or diabetes mellitus.

• Minorthese include breakthrough bleeding, weight gain, breast tenderness headache and nausea. Hirsutism and depression may occur following the combined OCP. Side-effects are lower in the progesterone only pill.

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