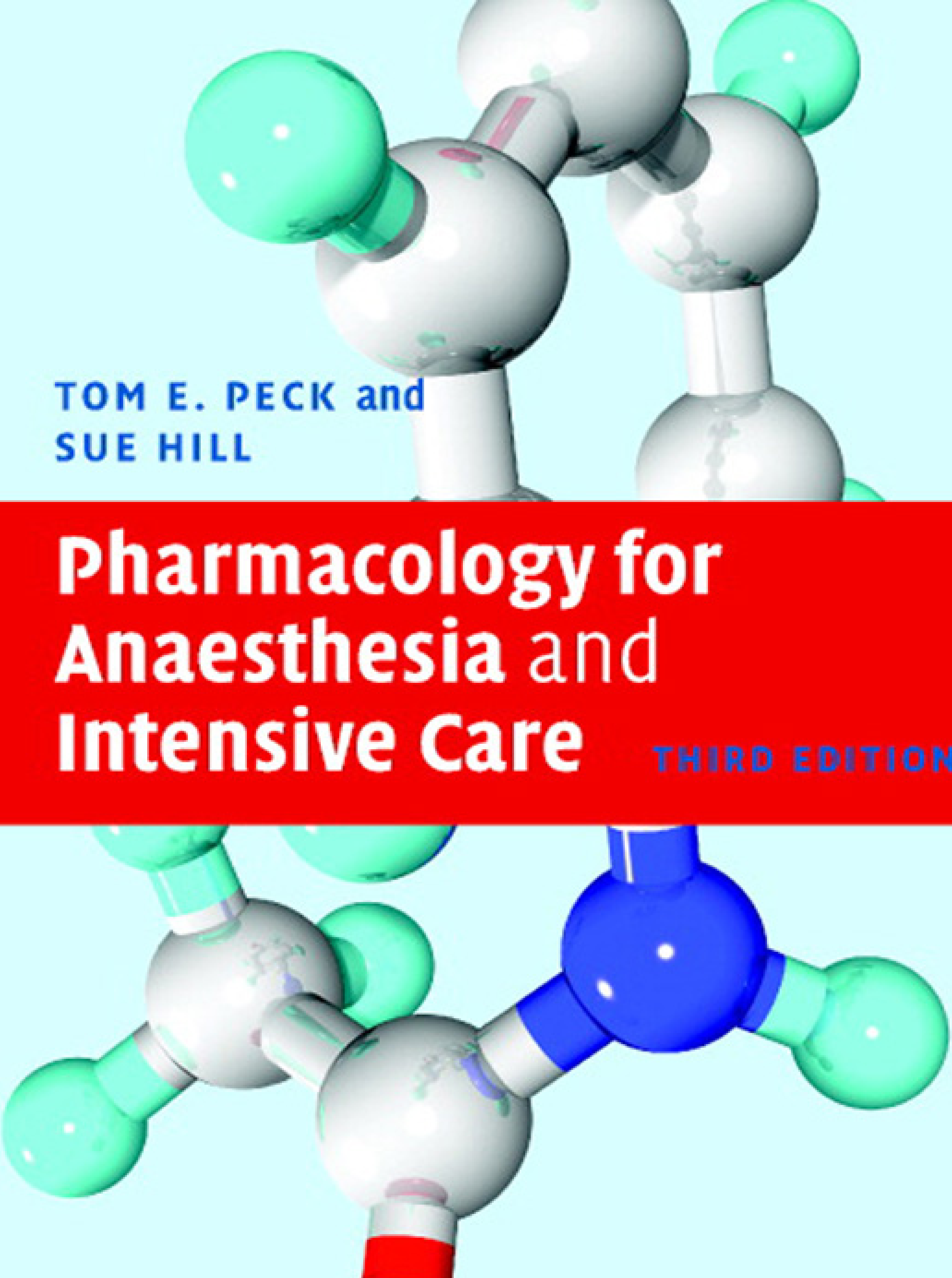

TOM E. PECK and
SUE HILL

# Pharmacology for Anaesthesia and Intensive Care

THIRD EDITION

CAMBRIDGE
Medicine

CAMBRIDGE

more information – www.cambridge.org/9780521704632

This page intentionally left blank

# Pharmacology for Anaesthesia and Intensive Care

THIRD EDITION

The third edition of this market-leading book has been thoroughly updated and expanded, with additional contributions from experts in the field, to include all new drugs available to the anaesthetist and intensive care specialist. Basic pharmacological principles, vital to understanding how individual drugs actually have their effects, are dealt with methodically and with many highly annotated diagrams and tables. With hospital infections becoming increasingly prevalent, the important section on antibiotics has been further expanded. With the third edition, this well established title continues to provide its readers with the most concise yet comprehensive coverage of all aspects of pharmacology. An ideal aid to study and practice for junior and trainee anaesthetists, critical care nurses and all physicians and healthcare professionals working in theatre, accident and emergency departments or intensive care units.

**Tom Peck** is a Consultant Anaesthetist at Royal Hampshire County Hospital, Winchester.

**Sue Hill** is a Consultant Neuroanaesthetist at Southampton General Hospital.

**Mark Williams** is a Consultant Anaesthetist at Royal Perth Hospital, Australia.

# Pharmacology for Anaesthesia and Intensive Care

THIRD EDITION

Tom Peck, Sue Hill and Mark Williams

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo, Delhi

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK
Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521704632

© Tom Peck Sue Hill and Mark Williams 2008

This publication is in copyright. Subject to statutory exception
and to the provisions of relevant collective licensing agreements,
no reproduction of any part may take place without
the written permission of Cambridge University Press.

First published 2000

Printed in the United Kingdom at the University Press, Cambridge

*A catalogue record for this publication is available from the British Library.*

*Library of Congress Cataloging-in-Publication Data*

Peck, T. E.
Pharmacology for anaesthesia and intensive care / Tom Peck, S. Hill, Mark Williams. – 3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-521-70463-2 (pbk.)
1. Pharmacology. 2. Anesthetics. 3. Anesthesia. 4. Critical care medicine.
I. Hill, S. A. (Sue A.) II. Williams, Mark (Mark Andrew) 1965- III. Title.
[DNLM: 1. Anesthetics–pharmacology. 2. Cardiovascular Agents–pharmacology.
3. Intensive Care. QV 81 P367p 2007]

RM300.P396 2007
615′.1–dc22 2007029048

ISBN 978-0-521-70463-2 paperback

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

# CONTENTS

*Preface* *page* ix
*Foreword* xi

SECTION I **Basic principles** 1
1 Drug passage across the cell membrane 1
2 Absorption, distribution, metabolism and excretion 8
3 Drug action 24
4 Drug interaction 40
5 Isomerism 45
6 Mathematics and pharmacokinetics 50
7 Medicinal chemistry 85

SECTION II **Core drugs in anaesthetic practice** 99
8 General anaesthetic agents 99
9 Analgesics 135
10 Local anaesthetics 163
11 Muscle relaxants and anticholinesterases 175

SECTION III **Cardiovascular drugs** 197
12 Sympathomimetics 197
13 Adrenoceptor antagonists 217
14 Anti-arrhythmics 228
15 Vasodilators 246
16 Antihypertensives 258

SECTION IV **Other important drugs** 270
17 Central nervous system 270
18 Antiemetics and related drugs 282
19 Drugs acting on the gut 292
20 Intravenous fluids 298
21 Diuretics 305
22 Antimicrobials 311
23 Drugs affecting coagulation 335

24 Drugs used in Diabetes 347
25 Corticosteroids and other hormone preparations 353

*Index* 360

# CONTRIBUTOR

**Dr. A.S. Grice, BSc, DCH, FRCA, Consultant Anaesthetist, Exeter**

# PREFACE

The third edition has seen further changes. The mathematics section has been overhauled and expanded to give a better base for the kinetics. An additional chapter has been added on intravenous fluids, and the chapters on intravenous and volatile anaesthetics have been combined with an expanded section on the molecular mechanism of anaesthesia.

We have tried to maintain the style of the previous two editions with an emphasis on clarity both in terms of presentation and content. In addition we have tried very hard to eliminate those small errors that are disproportionately irritating. We hope that this book will continue to be a helpful aid to the wide range of readers it appears to have attracted.

*Tom Peck*
*Sue Hill*
*Mark Williams*

# FOREWORD

I can remember my first day as an anaesthetic senior house officer, back in August 1985, and the advice that I received on that first day is still relevant for the twenty first century anaesthetist. “Anaesthesia is based on three basic sciences, physiology, physics and pharmacology,” said my first college tutor. The following weekend I took a trip to Lewis’s book shop in Gower Street to buy the recommended texts of the day. None of those I bought are still in print, but the pharmacology text has certainly been replaced by “Pharmacology for Anaesthesia and Intensive Care.”

The first two editions established themselves as the core pharmacology text for aspiring anaesthetists. It has evolved with each edition and the third edition has continued this trend, with some interesting new features. The mathematics and pharmacokinetics chapter is particularly well presented, and explains the concepts concisely and clearly. This is core knowledge that appears in the examinations of the Royal College of Anaesthetists but should be retained for all clinical anaesthetists and intensive care specialists.

Perhaps the title of the book should be changed for future editions as there has been a large change in medical education in the UK since the second edition, namely Modernising Medical Careers. This book is relevant to all foundation trainees who rotate through anaesthesia, intensive care and acute medical specialties. The new chapter on fluids is especially relevant to those at the start of their careers. The core knowledge presented should help to encourage good prescribing practice on all acute medical and surgical wards and avoid fluid management errors.

In summary the new edition is essential reading for those embarking on an anaesthetic career and is a core text for the FRCA. The authors come from district general and teaching hospital backgrounds but this book offers concise common sense pharmacology knowledge to all grades, even those who started anaesthesia before propofol was introduced!!

*Richard Griffiths MD FRCA*
*Consultant in Anaesthesia & Intensive Care Medicine*
*Peterborough & Stamford Hospitals NHS Trust.*
*Chairman of Structured Oral Examination I for the FRCA Pt I*

# SECTION I 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 hydrophilic heads on the outside and the lipophilic chains facing inwards. This gives a sandwich effect, with two hydrophilic layers surrounding the central hydrophobic one. Spanning this bilayer or attached to the outer or inner leaflets are glycoproteins, which may act as ion channels, receptors, intermediate messengers (G-proteins) 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). An exception to this is a specialized membrane area such as the neuromuscular junction, where the array of post-synaptic receptors is found opposite a motor nerve ending.

The general cell membrane structure is modified in certain tissues to allow more specialized functions. Capillary endothelial cells have fenestrae, which are regions of the endothelial cell where the outer and inner membranes are fused together, with no intervening cytosol. These make the endothelium of the capillary relatively permeable; fluid in particular can pass rapidly through the cell by this route. In the case of the renal glomerular endothelium, gaps or clefts exist between cells to allow the passage of larger molecules as part of filtration. Tight junctions exist between endothelial cells of brain blood vessels, forming the blood–brain barrier (BBB), intestinal mucosa and renal tubules. These limit the passage of polar 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).

## 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. Many drugs are weak acids or weak bases and can exist in either the unionized or ionized form, depending on the pH. The unionized form of a drug is lipid-soluble and diffuses easily by dissolution in the lipid bilayer. Thus the rate at which transfer occurs depends on

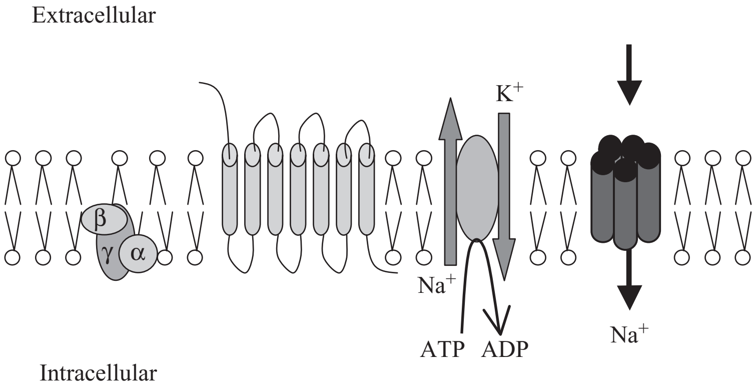

**Figure 1.1.** Representation of the cell membrane structure. The integral proteins embedded in this phospholipid bilayer are G-protein, G-protein-coupled receptors, transport proteins and ligand-gated ion channels. Additionally, enzymes or voltage-gated ion channels may also be present.

the p$K_a$ of the drug in question. Factors influencing the rate of diffusion are discussed below.

In addition, there are specialized **ion channels** in the membrane that allow intermittent passive movement of selected ions down a concentration gradient. When opened, ion channels allow rapid ion flux for a short time (a few milliseconds) down relatively large concentration and electrical gradients, which makes them suitable to propagate either ligand- or voltage-gated action potentials in nerve and muscle membranes.

The acetylcholine (ACh) receptor has five subunits (pentameric) arranged to form a central ion channel that spans the membrane (Figure 1.3). Of the five subunits, two (the $\alpha$ subunits) are identical. The receptor requires the binding of two ACh molecules to open the ion channel, allowing ions to pass at about $10^7$ $s^{-1}$. 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 $Na^+$. The $GABA_A$ receptor is also a pentameric, ligand-gated

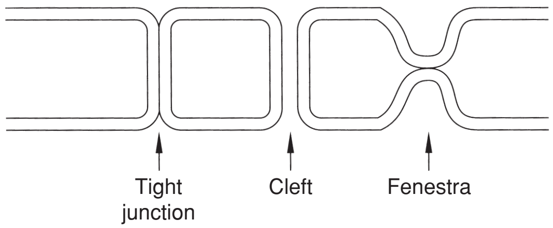

**Figure 1.2.** Modifications of the general cell membrane structure.

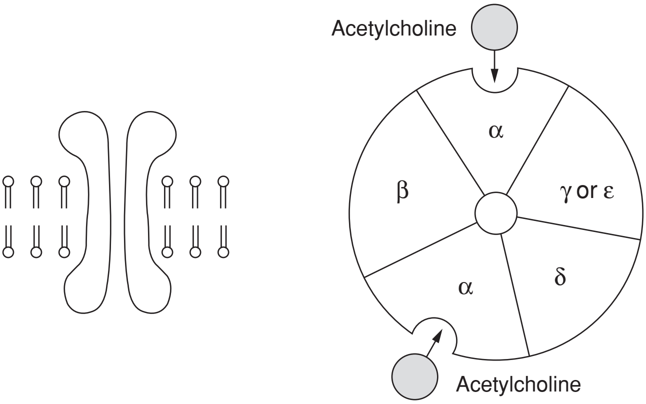

**Figure 1.3.** The acetylcholine (ACh) receptor has five subunits and spans the cell membrane. ACh binds to the $\alpha$ subunits, causing a conformational change and allowing the passage of small cations through its central ion channel. The $\epsilon$ subunit replaces the fetal-type $\gamma$ subunit after birth once the neuromuscular junction reaches maturity.

channel, but selective for anions, especially the chloride anion. The NMDA (N-methyl D-aspartate) receptor belongs to a different family of ion channels and is a dimer; it favours calcium as the cation mediating membrane depolariztion.

Ion channels may have their permeability altered by endogenous compounds or by drugs. Local anaesthetics bind to the internal surface of the fast $Na^+$ ion channel and prevent the conformational change required for activation, while non-depolarizing muscle relaxants prevent receptor activation by competitively inhibiting the binding of ACh to its receptor site.

## Facilitated diffusion

Facilitated diffusion refers to the process where molecules combine with membrane-bound carrier proteins to cross the membrane. The rate of diffusion of the molecule–protein complex is still down a concentration gradient but is faster than would be expected by diffusion alone. Examples of this process include the absorption of steroids and amino acids from the gut lumen. The absorption of glucose, a very polar molecule, would be relatively slow if it occurred by diffusion alone and requires facilitated diffusion to cross membranes (including the BBB) rapidly.

## Active transport

Active transport is an energy-requiring process. The molecule is transported against its concentration gradient by a molecular pump, which requires energy to function. Energy can be supplied either directly to the ion pump, or indirectly by coupling pump-action to an ionic gradient that is actively maintained. Active transport is encountered commonly in gut mucosa, the liver, renal tubules and the BBB.

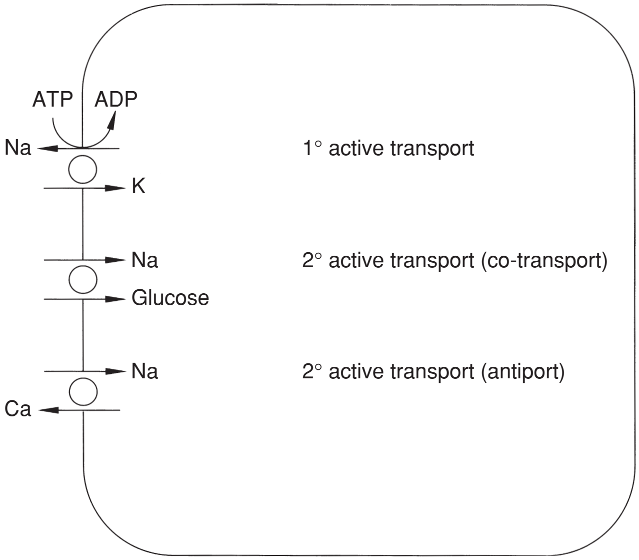
ATP
ADP
Na
K
1° active transport
Na
Glucose
2° active transport (co-transport)
Na
Ca
2° active transport (antiport)

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

$Na^+/K^+$ ATPase is an example of a direct energy-dependent pump – the 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 sodium moves in one direction and potassium in the opposite direction. The $Na^+$/amino acid symport (substances moved in the same direction) in the mucosal cells of the small bowel or on the luminal side of the proximal renal tubule is an example of secondary active transport. Here, amino acids will only cross the mucosal cell membrane when $Na^+$ is bound to the carrier protein and moves 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.

## 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 released into 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 (Figure 1.5).

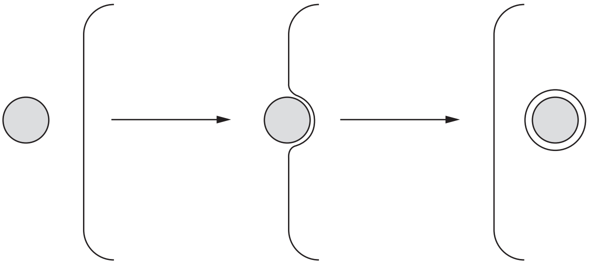

**Figure 1.5.** Pinocytosis.

## Factors influencing the rate of diffusion

### Molecular size

The rate of passive diffusion is inversely proportional to the square root of molecular size (Graham's law). In general, small molecules will diffuse much more readily than large ones. The molecular weights of anaesthetic agents are relatively small and anaesthetic agents diffuse rapidly through lipid membranes to exert their effects.

### Concentration gradient

Fick's law states that the rate of transfer across a membrane is proportional to the concentration gradient across the membrane. Thus 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. This is the basis of Bowman's principle, applied to the onset of action of non-depolarizing muscle relaxants. The less potent the drug, the more required to exert an effect – but this increases the concentration gradient between plasma and active site, so the onset of action is faster.

### Ionization

The lipophilic nature of the cell membrane only permits the passage of the uncharged fraction of any drug. The degree to which a drug is ionized in a solution depends on the molecular structure of the drug and the pH of the solution in which it is dissolved and is given by the Henderson–Hasselbalch equation.

The $\mathrm{pK_a}$ is the pH at which 50% of the drug molecules are ionized – thus the concentrations of ionized and unionized portions are equal. The value for $\mathrm{pK_a}$ depends on the molecular structure of the drug and is independent of whether it is acidic or basic.

The Henderson–Hasselbalch equation is most simply expressed as:

$$\mathrm{pH} = \mathrm{pK_a} + \log\left\{\frac{[\text{proton acceptor}]}{[\text{proton donor}]}\right\}.$$

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

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

with $X^-$ being the ionized form of an acid.

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

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

with $XH^+$ being the ionized form of a base.

Using the terms 'proton donor' and 'proton acceptor' instead of 'acid' or 'base' in the equation avoids confusion and the degree of ionization of a molecule may be readily established if its $pK_a$ and the ambient pH are known. At a pH below their $pK_a$ weak acids will be more unionized; at a pH above their $pK_a$ they will be more ionized. The reverse is true for weak bases, which are more ionized at a pH below their $pK_a$ and more unionized at a pH above their $pK_a$.

Bupivacaine is a weak base with a tertiary amine group in the piperidine ring. The nitrogen atom of this amine group is a proton acceptor and can become ionized, depending on pH. With a $pK_a$ of 8.1, it is 83% ionized at physiological pH.

Aspirin is an acid with a $pK_a$ of 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 increases its rate of absorption. However, because of 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; this property is independent of the $pK_a$ of the drug. However, high lipid solubility alone 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. This is a result of several factors. First, alfentanil is less potent and has a smaller distribution volume and therefore initially a greater concentration gradient exists between effect site and plasma. Second, both fentanyl and alfentanil are weak bases and alfentanil has a lower $pK_a$ than fentanyl (alfentanil = 6.5; fentanyl = 8.4), so that at physiological pH a much greater fraction of alfentanil is unionized and available to cross membranes.

Lipid solubility affects the rate of absorption from the site of administration. 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 the less lipid-soluble morphine remains in the cerebrospinal fluid 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; drugs vary greatly in the degree of plasma protein binding. In practice, the extent of this binding is of importance only if the drug is highly protein-bound (more than 90%). In these cases, small changes in the bound fraction produce large changes in the amount of unbound drug. In general, this increases the rate at which drug is metabolized, so a new equilibrium is re-established with little change in free drug concentration. For a very small number of highly protein-bound drugs where metabolic pathways are close to saturation (such as phenytoin) this cannot happen and plasma concentration of unbound drug will increase and possibly reach toxic levels.

Both albumin and globulins bind drugs, each has many binding sites, the number and characteristics of which are determined by the pH of plasma. In general, albumin binds neutral or acidic drugs (e.g. barbiturates), and globulins (in particular, $\alpha-1$ acid glycoprotein) bind basic drugs (e.g. morphine).

Albumin has two important binding sites: the warfarin and diazepam. Binding is usually readily reversible, and competition for binding at any one site between different drugs can alter the active unbound fraction of each. Binding is also possible at other sites on the molecule, which may cause a conformational change and indirectly influence binding at the diazepam and warfarin sites.

Although $\alpha-1$ acid glycoprotein binds basic drugs, other globulins are important in binding individual ions and molecules, particularly the metals. Thus, iron is bound to $\beta-1$ globulin and copper to $\alpha-2$ globulin.

Protein binding is altered in a range of pathological conditions. Inflammation changes the relative proportions of the different proteins and albumin concentration falls in any acute infective or inflammatory process. This effect is independent of any reduction in synthetic capacity resulting from liver impairment and is not due to protein loss. In conditions of severe hypoalbuminaemia (e.g. in 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. The magnitude of these effects may be hard to estimate and drug dose should be titrated against clinical effect.

# 2

# Absorption, distribution, metabolism and excretion

## Absorption

Drugs may be given by a variety of routes; the route chosen depends on the desired site of action and the type of drug preparations available. Routes used commonly by the anaesthetist include inhalation, intravenous, oral, intramuscular, rectal, epidural and intrathecal. Other routes, such as transdermal, subcutaneous and sublingual, also can be used. The rate and extent of absorption after a particular route of administration depends on both drug and patient factors.

Drugs may be given orally for local as well as systemic effects, for example, oral vancomycin used to treat pseudomembranous colitis is acting locally; antacids also act locally in the stomach. In such cases, systemic absorption may result in unwanted side effects.

Intravenous administration provides a direct, and therefore more reliable, route of systemic drug delivery. No absorption is required, so plasma levels are independent of such factors as gastrointestinal (GI) absorption and adequate skin or muscle perfusion. However, there are disadvantages in using this route. Pharmacological preparations for intravenous therapy are generally more expensive than the corresponding oral medications, and the initially high plasma level achieved with some drugs may cause undesirable side effects. In addition, if central venous access is used, this carries its own risks. Nevertheless, most drugs used in intensive care are given by intravenous infusion this way.

### Oral

After oral administration, absorption must take place through the gut mucosa. For drugs without specific transport mechanisms, only unionized drugs pass readily through the lipid membranes of the gut. Because the pH of the GI tract varies along its length, the physicochemical properties of the drug will determine from which part of the GI tract the drug is absorbed.

Acidic drugs (e.g. aspirin) are unionized in the highly acidic medium of the stomach and therefore are absorbed more rapidly than basic drugs. Although weak bases (e.g. propranolol) are ionized in the stomach, they are relatively unionized in the duodenum, so are absorbed from this site. The salts of permanently charged drugs (e.g. vecuronium, glycopyrrolate) remain ionized at all times and are therefore not absorbed from the GI tract.

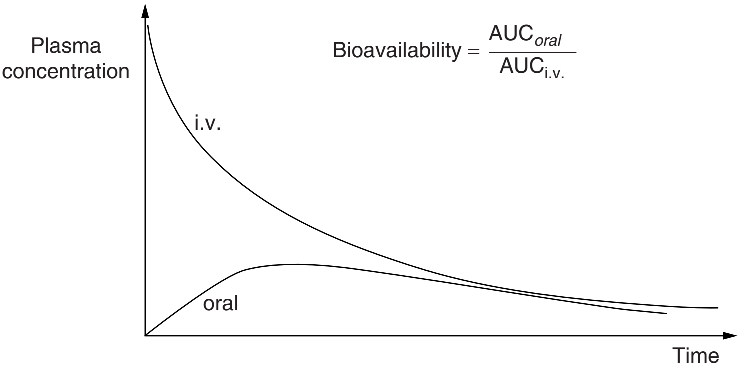

**Figure 2.1.** Bioavailability may be estimated by comparing the areas under the curves.

In practice, even acidic drugs are predominantly absorbed from the small bowel, as the surface area for absorption is so much greater due to the presence of mucosal villi. However, acidic drugs, such as aspirin, have some advantages over basic drugs in that absorption is initially rapid, giving a shorter time of onset from ingestion, and will continue even in the presence of GI tract stasis.

## Bioavailability

Bioavailability is generally defined as the fraction of a drug dose reaching the systemic circulation, compared with the same dose given intravenously (i.v.). In general, the oral route has the lowest bioavailability of any route of administration. Bioavailability can be found from the ratio of the areas under the concentration–time curves for an identical bolus dose given both orally and intravenously (Figure 2.1).

### Factors influencing bioavailability

- *Pharmaceutical preparation* – the way in which a drug is formulated affects its rate of 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 (e.g. enteric-coated preparations), absorption may be delayed.
- *Physicochemical interactions* – other 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 $Ca^{2+}$ such as in milk).
- *Patient factors* – various 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.
- *Pharmacokinetic interactions and first-pass metabolism* – drugs absorbed from the gut (with the exception of the buccal and rectal mucosa) pass via the portal

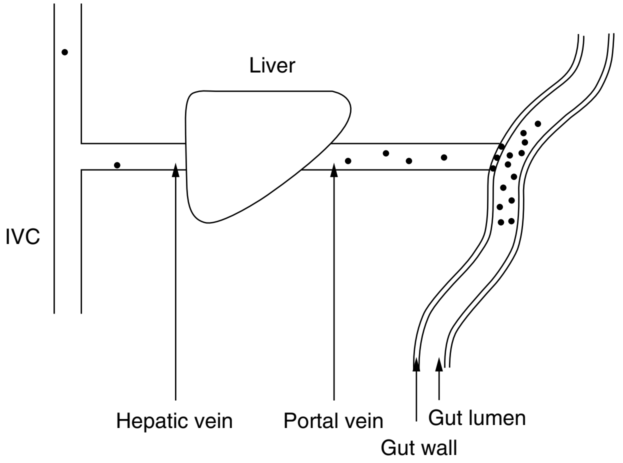

**Figure 2.2.** First-pass metabolism may occur in the gut wall or in the liver to reduce the amount of drug reaching the circulation.

vein to the liver where they may be subject to first-pass metabolism. Metabolism at either the gut wall (e.g. glyceryl trinitrate (GTN)) or liver will reduce the amount reaching the circulation. Therefore, an adequate plasma level may not be achieved orally using a dose similar to that needed intravenously. So, for an orally administered drug, the bioavailable fraction ($F_B$) is given by:

$$F_B = F_A \times F_G \times F_H.$$

Here $F_A$ is the fraction absorbed, $F_G$ the fraction remaining after metabolism in the gut mucosa and $F_H$ the fraction remaining after hepatic metabolism. Therefore, drugs with a high oral bioavailability are stable in the gastrointestinal tract, are well absorbed and undergo minimal first-pass metabolism (Figure 2.2). First-pass metabolism may be increased and oral bioavailability reduced through the induction of hepatic enzymes (e.g. phenobarbital induces hepatic enzymes, reducing the bioavailability of warfarin). Conversely, hepatic enzymes may be inhibited and bioavailability increased (e.g. cimetidine may increase the bioavailability of propranolol).

### Extraction ratio

The extraction ratio (ER) is that fraction of drug removed from blood by the liver. ER depends on hepatic blood flow, uptake into the hepatocyte and enzyme metabolic capacity within the hepatocyte. The activity of an enzyme is described by its Michaelis constant, which is the concentration of substrate at which it is working at 50% of its maximum rate. Those enzymes with high metabolic capacity have Michaelis constants very much higher than any substrate concentrations likely to be found clinically; those with low capacity will have Michaelis constants close to clinically relevant concentrations. Drugs fall into three distinct groups:

*Drugs for which the hepatocyte has rapid uptake and a high metabolic capacity,* for example, propofol and lidocaine. Free drug is rapidly removed from plasma, bound drug is released to maintain equilibrium and a concentration gradient is maintained between plasma and hepatocyte because drug is metabolized very quickly. Because protein binding has rapid equilibration, the total amount of drug metabolized will be independent of protein binding but highly dependent on liver blood flow.

*Drugs that have low metabolic capacity and high level of protein binding (>90%)*. This group includes phenytoin and diazepam. Their ER is limited by the metabolic capacity of the hepatocyte and not by blood flow. If protein binding is altered (e.g. by competition) then the free concentration of drug increases significantly. This initially increases uptake into the hepatocyte and rate of metabolism and plasma levels of free drug do not change significantly. However, if the intracellular concentration exceeds maximum metabolic capacity (saturates the enzyme) drug levels within the cell remain high, so reducing uptake (reduced concentration gradient) and ER. Those drugs with a narrow therapeutic index may then show significant toxic effects; hence the need for regular checks on plasma concentration, particularly when other medication is altered. Therefore for this group of drugs extraction is influenced by changes in protein binding more than by changes in hepatic blood flow.

*Drugs that have low metabolic capacity and low level of protein binding*. The total amount of drug metabolized for this group of drugs is unaffected by either by hepatic blood flow or by changes in protein binding.

## Sublingual

The sublingual, nasal and buccal routes have two advantages – they are rapid in onset and, by avoiding the portal tract, have a higher bioavailability. This is advantageous for drugs where a rapid effect is essential, for example, GTN spray for angina or sublingual nifedipine for the relatively rapid control of high blood pressure.

## Rectal

The rectal route can be used to avoid first-pass metabolism, and may be considered if the oral route is not available. Drugs may be given rectally for their local (e.g. steroids for inflammatory bowel disease), as well as their systemic effects (e.g. diclofenac suppositories for analgesia). There is little evidence that the rectal route is more efficacious than the oral route; it provides a relatively small surface area, and absorption may be slow or incomplete.

## Intramuscular

The intramuscular (i.m.) route avoids the problems associated with oral administration and the bioavailable fraction approaches 1.0. The speed of onset is generally more rapid compared with the oral route, and for some drugs approaches that for the intravenous route.

The rate of absorption depends on local perfusion at the site of i.m. injection. Injection at a poorly perfused site may result in delayed absorption and for this reason the well-perfused muscles deltoid, quadriceps or gluteus are preferred. If muscle perfusion is poor as a result of systemic hypotension or local vasoconstriction then an intramuscular injection will not be absorbed until muscle perfusion is restored. Delayed absorption will have two consequences. First, the drug will not be effective within the expected time, which may lead to further doses being given. Second, if perfusion is then restored, plasma levels may suddenly rise into the toxic range. For these reasons, the intravenous route is preferred if there is any doubt as to the adequacy of perfusion.

Not all drugs can be given i.m., for example, phenytoin. Intramuscular injections may be painful (e.g. cyclizine) and may cause a local abscess or haematoma, so should be avoided in the coagulopathic patient. There is also the risk of inadvertent intravenous injection of drug intended for the intramuscular route.

## Subcutaneous

Certain drugs are well absorbed from the subcutaneous tissues and this is the favoured route for low-dose heparin therapy. A further indication for this route is where patient compliance is a problem and depot preparations may be useful. Antipsychotic medication and some contraceptive formulations have been used in this way. Co-preparation of insulin with zinc or protamine can produce a slow absorption profile lasting several hours after subcutaneous administration.

As with the intramuscular route, the kinetics of absorption is 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 bolus once the perfusion is restored.

## Transdermal

Drugs may be applied to the skin either for local topical effect, such as steroids, but also may be used to avoid first-pass metabolism and improve bioavailability. Thus, fentanyl and nitrates may be given transdermally for their systemic effects. 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). Special transdermal formulations (patches) are used to ensure slow, constant release of drug for absorption and provide a smoother pharmacokinetic profile. Only small amounts of drug are released at a time, so potent drugs are better suited to this route of administration if systemic effects are required.

Local anaesthetics may be applied topically to anaesthetize the skin before venepuncture, skin grafts or minor surgical procedures. The two most common preparations are topical EMLA and topical amethocaine. The first is a eutectic mixture (each agent lowers the boiling point of the other forming a gel-phase) of lidocaine and prilocaine. Amethocaine is an ester-linked local anaesthetic, which may cause mild, local histamine release producing local vasodilatation, in contrast to the vasoconstriction seen with eutectic mixture of local anaesthetic (EMLA). Venodilatation may be useful when anaesthetizing the skin prior to venepuncture.

## Inhalation

Inhaled drugs may be intended for local or systemic 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 reaches the upper airways. Droplets of less than 1 micron diameter (which may be generated by an ultrasonic nebulizer) can reach the alveolus and hence the systemic circulation. However, a larger droplet or particle size reaches only airway mucosa from the larynx to the bronchioles (and often is swallowed from the pharynx) 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 resulting in unwanted systemic effects. Chronic use of inhaled steroids may lead to Cushingoid side effects, whereas high doses of inhaled $\beta_2$-agonists (e.g. salbutamol) may lead to tachycardia and hypokalaemia. Nebulized adrenaline, used for upper airway oedema causing stridor, may be absorbed and can lead to significant tachycardia, arrhythmias and hypertension, although catecholamines are readily metabolized by lung tissue. Similarly, sufficient quantities of topical lidocaine applied prior to fibreoptic intubation may be absorbed and cause systemic toxicity.

Inhaled nitric oxide reaches the alveolus and dilates the pulmonary vasculature. It is absorbed into the pulmonary circulation but does not produce unwanted systemic effects as it has a short half-life, as a result of binding to haemoglobin.

### Systemic site of action

The large surface area of the lungs (70 $m^2$ in an adult) available for absorption can lead to a rapid increase in systemic concentration and hence rapid onset of action at distant effect sites. Volatile anaesthetic agents are given by the inhalation route with their ultimate site of action the central nervous system.

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

## Epidural

The epidural route is used to provide regional analgesia and anaesthesia. Epidural local anaesthetics, opioids, ketamine and clonidine have all been used to treat acute pain, whereas steroids are used for diagnostic and therapeutic purposes in patients with chronic pain. Drug may be given as a single bolus or, through a catheter placed in the epidural space, as a series of boluses or by infusion.

The speed of onset of block is determined by the proportion of unionized drug available to penetrate the cell membrane. Local anaesthetics are bases with $pK_a$s greater than 7.4 so are predominantly ionized at physiological pH (see Chapter 1). Local anaesthetics with a low $pK_a$, such as lidocaine, will be less ionized and onset of the block will be faster than for bupivacaine, which has a higher $pK_a$. Thus lidocaine rather than bupivacaine is often used to 'top up' an existing epidural before surgery. Adding sodium bicarbonate to a local anaesthetic solution increases pH and the unionized fraction, further reducing the onset time. Duration of block depends on tissue binding; bupivacaine has a longer duration of action than lidocaine. The addition of a vasoconstrictor, such as adrenaline or felypressin, will also increase the duration of the block by reducing loss of local anaesthetic from the epidural space.

Significant amounts of drug may be absorbed from the epidural space into the systemic circulation especially during infusions. Local anaesthetics and opioids are both commonly administered via the epidural route and carry significant morbidity when toxic systemic levels are reached.

### Intrathecal

Compared with the epidural route, the amount of drug required when given intrathecally is very small; little reaches the systemic circulation and this rarely causes unwanted systemic effects. The extent of spread of a subararachnoid block with local anaesthetic depends on volume and type of solution used. Appropriate positioning of the patient when using hyperbaric solutions, such as with 'heavy' bupivacaine, can limit the spread of block.

## Distribution

Drug distribution depends on factors that influence the passage of drug across the cell membrane (see Chapter 1) and on regional blood flow. Physicochemical factors include: molecular size, lipid solubility, degree of ionization and protein binding. Drugs fall into one of three general groups:

- *Those confined to the plasma* – certain drugs (e.g. dextran 70) are too large to cross the vascular endothelium. Other drugs (e.g. warfarin) may be so intensely protein bound that the unbound fraction is tiny, so that the amount available to leave the circulation is immeasurably small.
- *Those with limited distribution* – the 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. They cannot cross cell membranes but work extracellularly.
- *Those with extensive distribution* – these drugs are often highly lipid-soluble. Providing their molecular size is relatively small, the extent of plasma protein binding does not restrict their distribution due to the weak nature of such interactions.

Other drugs are sequestered by tissues (amiodarone by fat; iodine by the thyroid; tetracyclines by bone), which effectively removes them from the circulation.

Those drugs that are not confined to the plasma are initially distributed to tissues with the highest blood flow (brain, lung, kidney, thyroid, adrenal) then to tissues with a moderate blood flow (muscle), and finally to tissues with a very low blood flow (fat). These three groups of tissues provide a useful model when explaining how plasma levels decline after drug administration.

## Blood–brain barrier (BBB)

The BBB is an anatomical and functional barrier between the circulation and the central nervous system (see Chapter 1).

Active transport and facilitated diffusion are the predominant methods 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. Thus inhaled and intravenous anaesthetics can cross readily whereas the larger, polar muscle relaxants cannot and have no central effect. Similarly, glycopyrrolate has a quaternary, charged nitrogen and does not cross the BBB readily. This is in contrast to atropine, a tertiary amine, which may cause centrally mediated effects such as confusion or paradoxical 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 may help 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 permeability to penicillin (and other drugs) increases, so allowing therapeutic access.

## Drug distribution to the fetus

The placental membrane that separates fetal and maternal blood is initially derived from adjacent placental syncytiotrophoblast and fetal capillary membranes, 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. It is much 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 (fetal) blood. Placental blood flow and the free drug concentration gradient between maternal and fetal blood determine the rate at which drug equilibration takes place. The pH of fetal blood is lower than that of the mother and fetal plasma protein binding may therefore differ. High protein binding in the fetus increases drug transfer across the placenta since fetal free drug levels are low. In contrast, high protein binding in the mother reduces the rate of drug transfer since maternal free drug levels are low. The fetus also may metabolize some drugs; the rate of metabolism increases as the fetus matures.

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

## Drugs during pregnancy

The safety of any drug in pregnancy must be evaluated, but interspecies variation is great and animal models may not exclude the possibility of significant human teratogenicity. In addition, teratogenic effects may not be apparent for some years; stilboestrol taken during pregnancy predisposes female offspring to ovarian cancer at puberty. Wherever possible drug therapy should be avoided throughout pregnancy; if treatment is essential drugs with a long history of safety should be selected.

There are conditions, however, in which the risk of not taking medication outweighs the theoretical or actual risk of teratogenicity. Thus, in epilepsy the risk of hypoxic damage to the fetus secondary to fitting warrants the continuation of anti-epileptic medication during pregnancy. Similarly, the presence of an artificial heart valve mandates the continuation of anticoagulation despite the attendant risks.

## Drugs at the time of birth

The newborn may have anaesthetic or analgesic drugs in their circulation depending on the type of analgesia for labour and whether delivery was operative. Drugs with a low molecular weight that are lipid-soluble will be present in higher concentrations than large polar molecules.

Bupivacaine is the local anaesthetic most commonly used for epidural analgesia. It crosses the placenta less readily than does lidocaine as its higher $pK_a$ makes it more ionized than lidocaine at physiological pH. However, the fetus is relatively acidic with respect to the mother, and if the fetal pH is reduced further due to placental insufficiency, the phenomenon of ion trapping may become significant. The fraction of ionized bupivacaine within the fetus increases as the fetal pH falls, its charge preventing it from leaving the fetal circulation, so that levels rise toward toxicity at birth.

Pethidine is commonly used for analgesia during labour. The high lipid solubility of pethidine enables significant amounts to cross the placenta and reach the fetus. It is metabolized to norpethidine, which is less lipid-soluble and can accumulate in the fetus, levels peaking about 4 hours after the initial maternal intramuscular dose. Owing to reduced fetal clearance the half-lives of both pethidine and norpethidine are prolonged up to three times.

Thiopental 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 fetal) levels occur within

3 minutes of maternal injection. There is no evidence that fetal outcome is affected with an'injection to delivery' time of up to 20 minutes after injection of a sleep dose of thiopental to the mother.

The non-depolarizing muscle relaxants are large polar molecules and essentially do not cross the placenta. Therefore, the fetal 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 fetus has also inherited the enzyme defect, in which case there may be a degree of depolarizing blockade at the fetal neuromuscular junction.

## Metabolism

While metabolism usually reduces the activity of a drug, activity may be designed to increase; a prodrug is defined as a drug that has no inherent activity before metabolism but that is converted by the body to an active moiety. Examples of prodrugs are enalapril (metabolized to enaloprilat), diamorphine (metabolized to 6-monoacylmorphine), and parecoxib (metabolized to valdecoxib). Metabolites also may have equivalent activity to the parent compound, in which case duration of action is not related to plasma levels of the parent drug.

In general, metabolism produces a more polar (water soluble) molecule that can be excreted in the bile or urine – the chief routes of drug excretion. There are two phases of metabolism, I and II.

### Phase I (functionalization or non-synthetic)

- Oxidation
- Reduction
- Hydrolysis

Many phase I reactions, particularly oxidative pathways, occur in the liver due to a non-specific mixed-function oxidase system in the endoplasmic reticulum. These enzymes form the cytochrome P450 system, named after the wavelength (in nm) of their maximal absorption of light when the reduced state is combined with carbon monoxide. However, this cytochrome system is not unique to the liver; these enzymes are also found in gut mucosa, lung, brain and kidney. Methoxyflurane is metabolized by CYP2E1 in the kidney, generating a high local concentration of fluoride ions, which may cause renal failure (see sevoflurane metabolism, p. 123).

The enzymes of the cytochrome P450 system are classified into families and subfamilies by their degree of shared amino acid sequences – families and subfamilies share 40% and 55% respectively of the amino acid sequence. In addition, the subfamilies are further divided into isoforms. Families are labelled CYP1, CYP2, and so on, the subfamilies CYP1A, CYP1B, and so on, and the isoforms CYP1A1, CYP1A2, and so on. Table 2.1 summarises isoenzymes of particular importance in the metabolism

**Table 2.1.** Metabolism of drugs by cytochrome P450 system.
CYP2C9 and CYP2D6 both demonstrate significant genetic polymorphism; other cytochromes also have variants, but these two are clinically important. Both losartan and parecoxib are prodrugs, so poor activity of CYP2C9 will limit active product availability.

| CYP2B6 | CYP2C9 | CYP2C19 | CYP2D6 | CYP2E1 | CYP3A4 | CYP3A5 |
|---|---|---|---|---|---|---|
| propofol | propofol<br>parecoxib<br>losartan<br>S-warfarin | losartan<br>diazepam<br>phenytoin<br>omeprazole | codeine<br>flecainide<br>metopropol | sevoflurane<br>halothane<br>isoflurane<br>paracetamol | diazepam<br>temazepam<br>midazolam<br>fentanyl<br>alfentanil<br>lidocaine<br>vecuronium | diazepam |

of drugs relevant to the anaesthetist. Many drugs are metabolized by more than one isozyme (e.g. midazolam by CYP3A4 and CYP3A5). Genetic variants are also found, in particular CYP2D6 and CYP2C9; a variant of CYP2D6 is associated with defective metabolism of codeine.

The P450 system is not responsible for all phase I metabolism. The monoamines (adrenaline, noradrenaline, dopamine) 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. Ethanol is metabolized by the cytoplasmic enzyme alcohol dehydrogenase to acetaldehyde, which is then further oxidized to acetic acid. This enzyme is one that is readily saturated, leading to a rapid increase in plasma ethanol if consumption continues. Esterases are also found in the cytoplasm of a variety of tissues, including liver and muscle, and are responsible for the metabolism of esters, such as etomidate, aspirin, atracurium and remifentanil. The lung also contains an angiotensin-converting enzyme that is responsible for AT1 to AT2 conversion; this enzyme is also able to break down bradykinin.

In addition, some metabolic processes take place in the plasma: cis-atracurium breaks down spontaneously in a pH- and temperature-dependent manner – Hofmann degradation – and suxamethonium is hydrolyzed by plasma cholinesterase.

## Phase II (conjugation or synthetic)

- Glucuronidation (e.g. morphine, propofol)
- Sulphation (e.g. quinol metabolite of propofol)
- Acetylation (e.g. isoniazid, sulphonamides)
- Methylation (e.g. catechols, such as noradrenaline)

Although many drugs are initially metabolized by phase I processes followed by a phase II reaction, some drugs are modified by phase II reactions only. Phase II reactions increase the water solubility of the drug or metabolite 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, such as lorazepam, are less affected.

### Genetic polymorphism

There are inherited differences in enzyme structure that alter the way drugs are metabolized in the body. The genetic polymorphisms of particular relevance to anaesthesia are those of plasma cholinesterase, those involved in acetylation and the CYP2D6 variants mentioned above.

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 the degree of enzyme inhibition demonstrated in vitro by substances such as fluoride and the local anaesthetic dibucaine. Muscle paralysis due to suxamethonium may be prolonged in individuals with an abnormal form of the enzyme. This is discussed in greater detail in Chapter 11.

Acetylation is a phase II metabolic pathway in the liver. Drugs metabolized by this route include hydralazine and isoniazid. There are genetically different isoenzymes that acetylate at a slow or fast rate. The pharmacokinetic and hence pharmacodynamic profile seen with these drugs depends on the acetylator status of the individual.

### Enzyme inhibition and induction

Some drugs (Table 2.2) induce the activity of the hepatic microsomal enzymes. 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 (e.g. cimetidine), 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 contributions from different routes of excretion depend upon the structure and molecular weight of a drug. In general, high molecular weight

**Table 2.2.** Effects of various drugs on hepatic microsomal enzymes.

| | Inducing | Inhibiting |
|---|---|---|
| Antibiotics | rifampicin | metronidazole, isoniazid, chloramphenicol acute use |
| Alcohol | chronic abuse | |
| Inhaled anaesthetics | enflurane, halothane | |
| Barbiturates | phenobarbital, thiopental | |
| Anti-convulsants | phenytoin, carbamazepine | |
| Hormones | glucocorticoids | |
| MAOIs | | phenelzine, tranylcypromine |
| $H_2$ antagonists | | cimetidine |
| Others | cigarette smoking | amiodarone, grapefruit juice |

compounds (>30 000) are not filtered or secreted by the kidney and are therefore preferentially excreted in the bile. A significant fraction of a drug carrying a permanent charge, such as pancuronium, may be excreted unchanged in urine.

## Renal excretion

### Filtration at the glomerulus

Small, non-protein bound, poorly lipid-soluble but readily water-soluble drugs are excreted into the glomerular ultrafiltrate. Only free drug present in that fraction of plasma that is filtered is removed at the glomerulus. The remaining plasma will have the same concentration of free drug as that fraction filtered and so there is no change in the extent of plasma protein binding. Thus highly protein bound drugs are not extensively removed by filtration – but may be excreted by active secretory mechanisms in the tubule.

### Secretion at the proximal tubules

There are active energy-requiring processes in the proximal convoluted tubules by which a wide variety of molecules may be secreted into the urine against their concentration gradients. Different carrier systems exist for acidic and basic drugs that are each capacity-limited for their respective 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 also may be inhibited, for example, 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 re-absorbed. 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 (e.g. morphine metabolites are excreted as glucuronides).

#### Enterohepatic circulation

Drugs excreted in the bile such as glucuronide conjugates may be hydrolyzed in the small bowel by glucuronidase secreted by bacteria. Lipid-soluble, active drug may result and be reabsorbed, passing into the portal circulation to the liver where the extracted fraction is reconjugated and re-excreted in the bile, and the rest passes into the systemic circulation. 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 dependent upon renal excretion – in the case of a drug whose clearance is entirely renal a single dose may have a very prolonged effect. This was true of gallamine, a non-depolarizing muscle relaxant, which, if given in the context of renal failure, required dialysis or haemofiltration to reduce the plasma level and hence reverse the pharmacological effect.

If it is essential to give a drug that is highly dependent on renal excretion 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 repeated doses may need to be reduced and dosing interval increased. However, due to fluid retention the volume of distribution is often increased in renal failure, so loading doses may be higher than in health.

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:

$$D = \text{Usual dose} \times (\text{impaired clearance}/\text{normal clearance}).$$

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 alters many aspects of the pharmacokinetic profile of a drug. 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 is reduced. The presence of ascites increases the volume of distribution and the presence of portocaval shunts increases bioavailability by reducing hepatic clearance of drugs.

There is no analogous measure of hepatic function compared with creatinine clearance for renal function. Liver function tests in common clinical use may be divided into those that measure the synthetic function of the liver – the international normalized ratio (INR) or prothrombin time and albumin – and those that measure inflammatory damage of the hepatocyte. It is possible to have a markedly inflamed liver with high transaminase levels, with retention of reasonable synthetic function. In illness, the profile of protein synthesis shifts toward acute phase proteins; albumin is not an acute phase protein so levels are reduced 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 careful intravenous titration of opioid analgesics, 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; the neonatal liver is relatively larger than that of an adult although its metabolizing capacity is lower and may not be as efficient.

#### Distribution

Plasma protein levels and binding are less than in the adult. In addition, the pH of neonatal blood tends to be 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 at adult levels, 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 differences may be predicted, the precise doses of drugs used in the newborn has largely been determined clinically. Preferred drugs should be those 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 post-conceptual age.

## Elderly

A number of factors contribute to pharmacokinetic differences observed in the elderly. The elderly have a relative reduction in muscle mass, with a consequent increase in the proportion of fat, altering volume of distribution. This loss of muscle mass is of great importance in determining the sensitivity of the elderly to remifentanil, which is significantly metabolized by muscle esterases. 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, reflecting reduced renal function.

As well as physiological changes with increasing age, the elderly are more likely to have multiple co-existing diseases. The implications of this are two-fold. First, the disease processes may directly alter drug pharmacokinetics and second, polypharmacy may produce drug interactions that alter both pharmacokinetics and pharmacodynamic response.

# 3

# Drug action

## Mechanisms of drug action

Drugs may act in a number of ways to exert their effect. These range from relatively simple non-specific actions that depend on the physicochemical properties of a drug to highly specific and stereoselective actions on proteins in the body, namely enzymes, voltage-gated ion channels and receptors.

## Actions dependent on chemical properties

The antacids exert their effect by 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 new reversal agent, $\gamma$-cyclodextrin, selectively chelates rocuronium and reversal is possible from deeper levels of block than can be effected with the anticholinesterases.

## Enzymes

Enzymes are biological catalysts, and most drugs that interact with enzymes are inhibitors. The results are twofold: the concentration of the substrate normally metabolized by the enzyme is increased and that of the product(s) of the reaction is decreased. Enzyme inhibition may be competitive (edrophonium for anticholinesterase), non-competitive or irreversible (aspirin for cyclo-oxygenase and omeprazole for the $Na^+/H^+$ATPase). Angiotensin-converting enzyme (ACE) inhibitors such as captopril prevent the conversion of angiotensin I to II and bradykinin to various inactive fragments. Although 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.

## Voltage-gated ion channels

Voltage-gated ion channels are involved in conduction of electrical impulses associated with excitable tissues in muscle and nerve. Several groups of drugs have specific blocking actions at these ion channels. Local anaesthetics act by inhibiting $Na^+$ channels in nerve membrane, several anticonvulsants block similar channels in the brain, calcium channel blocking agents act on vascular smooth muscle ion channels and antiarrhythmic agents block myocardial ion channels. These actions are described in the relevant chapters in Sections II and III.

## Receptors

A receptor is a protein, often integral to a membrane, containing a region to which a natural ligand binds specifically to bring about a response. A drug acting at a receptor binds to a recognition site where it may elicit an effect (an agonist), prevent the action of a natural ligand (an inhibitor), or reduce a constitutive effect of a receptor (an inverse agonist). Natural 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 $\gamma$-aminobutyric acid (GABA) at $GABA_A$ and $GABA_B$ receptors).

Receptors are generally protein or glycoprotein in nature and may be associated with or span the cell membrane, be present in the membranes of intracellular organelles or be found in the cytosol or nucleus. Those in the membrane are generally for ligands that do not readily penetrate the cell, whereas those within the cell are for lipid-soluble ligands that can diffuse through the cell wall to their site of action, or for intermediary messengers generated within the cell itself.

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

Receptors of this type are part of a membrane-spanning complex of protein subunits that have the potential to form a channel through the membrane. When opened, such a channel allows the passage of ions down their concentration and electrical gradients. Here, ligand binding causes a conformational change in the structure of this membrane protein complex allowing the channel to open and so increasing the permeability of the membrane to certain ions (ionotropic). There are three important ligand-gated ion channel families: the pentameric, the ionotropic glutamate, and the ionotropic purinergic receptors.

#### The pentameric family

The pentameric family of receptors has five membrane-spanning subunits. The best-known example of this type of ion channel receptors is the nicotinic acetylcholine receptor at the neuromuscular junction. It consists of one $\beta$, one $\epsilon$, one $\gamma$ and two $\alpha$ subunits. Two acetylcholine molecules bind to the $\alpha$ subunits, resulting in a rapid increase in $Na^+$ flux through the ion channel formed, leading to membrane depolarization.

Another familiar member of this family is the $GABA_A$ receptor, in which GABA is the natural ligand. Conformational changes induced when the agonist binds causes a chloride-selective ion channel to form, leading to membrane hyperpolarization. The benzodiazepines (BDZs) can influence GABA activity at this receptor but augment chloride ion conductance by an allosteric mechanism (see below for explanation).

The 5-$HT_3$ receptor is also a member of this pentameric family; it is the only serotonin receptor to act through ion-channel opening.

### Ionotropic glutamate

Glutamate is an excitatory neurotransmitter in the central nervous system (CNS) that works through several receptor types, of which NMDA, AMPA, and Kainate are ligand-gated ion channels. The NMDA receptors are comprised of two subunits, one pore-forming (NR1) and one regulatory that binds the co-activator, glycine (NR2). In vivo, it is thought that the receptors dimerize, forming a complex with four subunits. Each NR1 subunit has three membrane-spanning helices, two of which are separated by a re-entrant pore-forming loop. NMDA channels are equally permeable to $Na^+$ and $K^+$ but have a particularly high permeability to the divalent cation, $Ca^{2+}$. Ketamine, xenon and nitrous oxide are non-competitive antagonists at these receptors.

### Ionotropic purinergic receptors

This family of receptors includes PX1 and PX2. Each has two membrane-spanning helices and no pore-forming loops. They form cationic channels that are equally permeable to $Na^+$ and $K^+$ but are also permeable to $Ca^{2+}$. These purinergic receptors are activated by ATP and are involved in mechanosensation and pain. These are not to be confused with the two G-protein coupled receptor forms of purinergic receptors, which are distinguished by selectivity for adenosine or ATP.

## 2) Production of intermediate messengers

There are several membrane-bound systems that transduce a ligand-generated signal presented on one side of the cell membrane into an intracellular signal transmitted by intermediate messangers. The most common is the G-protein coupled receptor system but there are others including the tyrosine kinase and guanylyl cyclase systems.

### G-protein coupled receptors (GPCRs) and G-proteins

GPCRs are membrane-bound proteins with a serpentine structure consisting of seven helical regions that traverse the membrane. G-proteins are a group of heterotrimeric (three different subunits, $\alpha$, $\beta$ and $\gamma$) proteins associated with the inner leaflet of the cell membrane that act as universal transducers involved in bringing about an intracellular change from an extracellular stimulus. The GPCR binds a ligand on its extracellular side and the resultant conformational change increases the likelihood of coupling with a particular type of G-protein resulting in activation of intermediate messengers at the expense of GTP (guanylyl triphosphate) breakdown. This type of receptor interaction is sometimes known as **metabotropic** in contrast