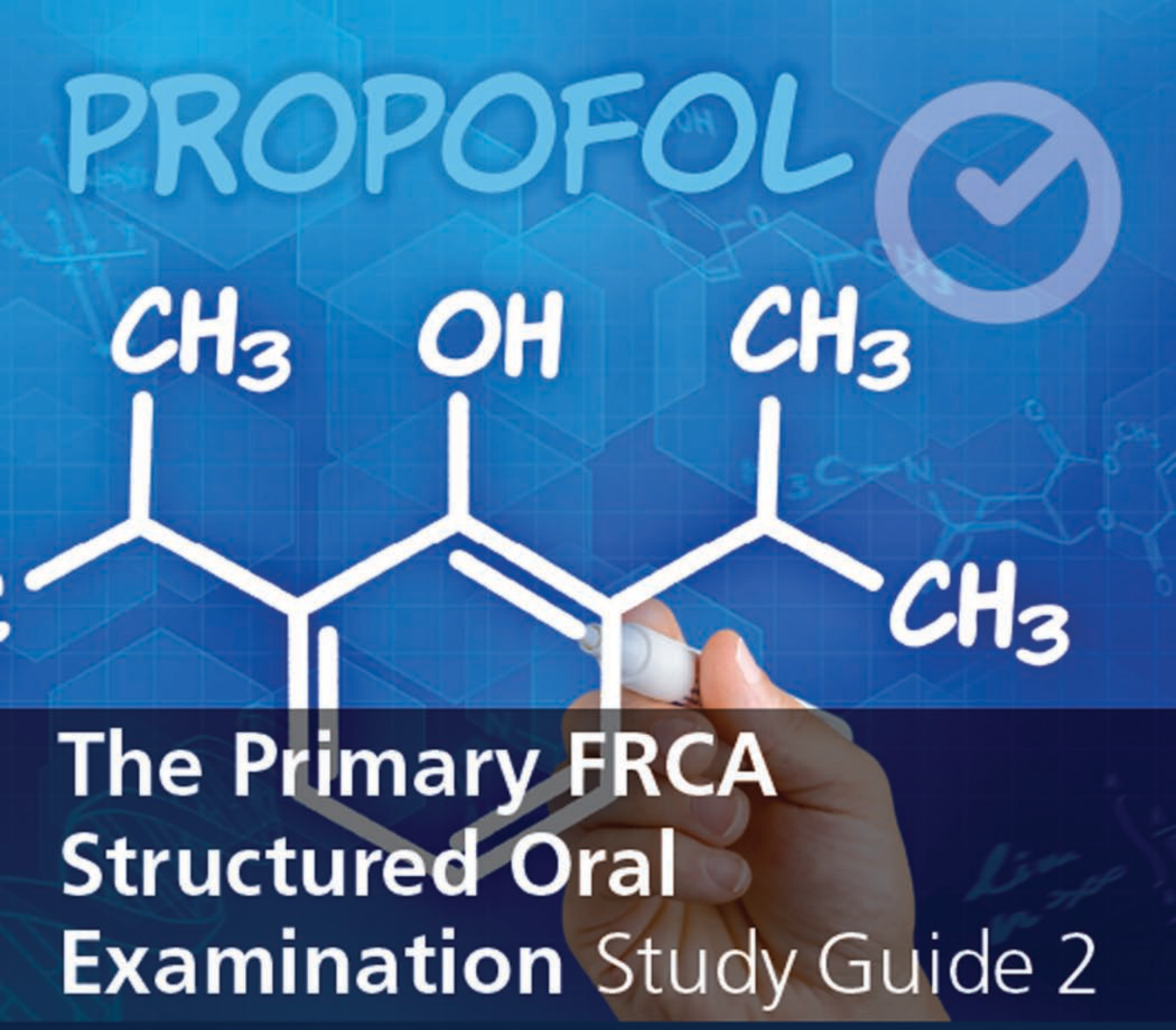

The Primary FRCA Structured Oral Examination Study Guide 2

Second Edition

Kate McCombe and Lara Wijayasiri

Illustrations by Paul Hatton • Foreword by David Bogod

CRC Press
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FOREWORD

Much has happened since I wrote the Foreword to the first edition of this invaluable guide to the Primary FRCA Structured Oral Examination in 2010. Of the three original authors, two have married (each other) and produced a baby girl. One of these two has had to relinquish the authorship of this new edition, since his promotion to the ranks of Primary Examiner unsurprisingly bars him from writing a book on how to pass the Primary exam. The two remaining authors have both moved up the ranks and been appointed as consultants, one with an interest in obstetrics, ethics and law, and the other specialising in vascular anaesthesia and the difficult airway. The first edition, meanwhile, has rapidly become the best-selling textbook on the Primary SOE. If a soap opera was ever to be based around the publication of a guide to passing post-graduate anaesthetic exams – admittedly an unlikely proposition – the story of McCombe and Wijayasiri would surely rival 'EastEnders' for intrigue and plot development.

In this new edition, as well as updating existing topics, the authors have included substantial additions to what was already a very comprehensive book, in line with changes made by the Royal College to the Primary syllabus. The section on 'special patient groups' now includes paediatrics and the elderly, the latter of increasingly personal interest to this writer. The section on physics – often a stumbling block for the Primary candidate – has been extensively revised and now covers those perennial favourites of the examiners, arterial waveforms and vaporisers; as one reads these, there are frequent 'aha!' moments, not least with respect to critical damping, the pumping effect and the influence of altitude on performance. Mindful of the old adage that 'a picture paints a thousand words', the authors have enhanced the number and quality of diagrams and figures, helping to clarify areas such as fetal circulation and the Kreb's cycle.

Some aspects of these books remain, thankfully, unchanged, in particular the resolutely pragmatic approach that McCombe and Wijayasiri take to help readers through the tangled thickets of the Primary. Here are the questions the examiners like to ask, the authors seem to say, and this is how to answer them. It is, perhaps, a tribute to the exam syllabus itself that this approach results in a textbook that is not only very readable but also highly educational.

In short, if you are not lucky enough to be working in the same hospital as the authors and you cannot approach them for viva practice (or even if you can), then the new edition of this book is an essential companion and a true *vade mecum*. Look it up – a bit of Latin can still impress the examiners!

David Bogod
Consultant Anaesthetist and Ex-Editor-in-Chief of *Anaesthesia*
Nottingham

PREFACE

During our revision for the primary exam we were advised that the best way to ensure success in the structured oral examination (SOE) was to prepare answers to all of the questions in the back of *The Royal College of Anaesthetists Guide to the FRCA Examination, The Primary*. Undoubtedly, this was excellent advice but it proved an enormous task and one we simply did not have time to complete before our own exams. However, once they were over, we began to answer all those questions in the hope that this might help others to prepare for the Primary, or for the basic science component of the Final FRCA. Finally then, here is the result: the book we wish we'd had.

The Primary FRCA Structured Oral Examination Study Guide provides answers to the questions regularly posed by the examiners. We have not attempted to write the next great anaesthetic textbook, but rather to collate information and deliver it in a relevant and userfriendly layout to make your exam preparation a little easier.

In the SOE itself, each topic will be examined for approximately five minutes. Many of these answers contain much more information than could reasonably be expected of you in that time; however, we have tried to cover several angles of questioning.

We have included the usual chapters on physiology, pharmacology (*Study Guide 1*) and physics (*Study Guide 2*) and, in addition, have written a section on patients who present the anaesthetist with unique problems, 'special patient groups' (*Study Guide 2*). These patients tend to appear in the clinical SOE before some terrible 'critical incident' befalls them. Again, we have included a section addressing the 'critical incidents' beloved of the examiner, with advice as to how to approach them in the SOE (*Study Guide 2*).

There is a unique pharmacology section including information on drugs commonly examined presented in a spider diagram layout. These extremely visual learning aids allowed us to revise the drugs in the necessary detail, and helped us to recall the information even under the acute stress of the exam. We hope you find them just as useful.

We wish you every success in what is undoubtedly a rigorous exam. We believe the key to this success is to practise presenting the knowledge that you already have, logically and concisely. The only way to do this is to practise speaking, even though the possibility of exposing any ignorance is daunting. The more you talk, the more you will cover, and every question is so much easier to answer in the exam if you have already had a dress rehearsal. We hope this book will help you in your preparations.

Good luck!

Lara Wijayasiri
Kate McCombe
December 2015

To Andrew, who makes me believe anything is possible.

Kate McCombe

To Amish, my husband and best friend- thank you for giving me the time to complete this book. And to Maya, my beautiful daughter- thank you for giving me a greater focus in life other than this book.

Lara Wijayasiri

CONTRIBUTORS

Paul Hatton B.Tec
Illustrations

Dr Barbara Lattuca MBBCh MRCP FRCA
Locum Consultant Anaesthetist, St George's NHS Healthcare Trust

Pharmacology
- Drugs and the kidney
- Inhalational anaesthetic agents (volatile agents)
- Antiplatelet agents
- Hypoglycaemic agents
- Antidepressants

Special patient groups
- Diabetes

Lt Col Mark Wyldbore MBBS BSc(Hons) FRCA RAMC
Consultant Anaesthetist, Queen Victoria Hospital NHS Foundation Trust

Pharmacology
- Drugs and the liver
- Total intravenous anaesthesia
- Anticoagulants

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Dr Tim Case MBBChir MPhil MA(Cantab)
Our sincerest thanks go to Tim for his eagle eyes and enviable grasp of physics. The book is better for his meticulous reading and attention to detail!

Part 01

PHARMACOLOGY

1. RECEPTORS

Define 'receptor' and 'ligand'.

Receptors are proteins, usually integral to the cell membrane, with selective ligand-binding sites.

A **ligand** is any substance able to bind to a receptor and bring about biological change within the cell. A ligand may be capable of binding to more than one receptor and exerting different effects at each different one.

What governs drug–receptor interactions?

The **law of mass action** governs drug–receptor interactions and so the rate of interaction is proportional to the concentration of drug and receptor. It is a specific, dose-dependent and saturatable interaction.

What are the different classes of receptors?

Table 1.1 Receptor classes

Receptor	Ligand-gated ion channel receptor	G-protein-coupled receptor	Tyrosine kinase linked receptor	Intracellular nuclear receptors
Location	Membrane	Membrane	Membrane	Cytosol
Effector	Channel	Enzyme/Channel	Tyrosine kinase	Gene transcription
Coupling	Direct	G protein	Direct	via DNA
Speed	Milliseconds	Seconds	Minutes	Hours
Examples	nAChR $GABA_A$	mAChR Adrenoceptors	Insulin receptor	Thyroxine receptor Steroid receptor

What are the main mechanisms of receptor action?

> **Altered ion permeability:**
- Acetylcholine (ACh) binds to the two α subunits of the pentameric nicotinic acetylcholine receptor (nAChR), causing a conformational change, which opens a central pore allowing an influx of Na^+ ions, leading to cell depolarisation.

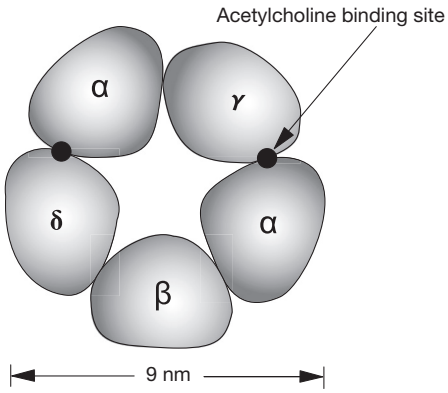


Fig. 1.1 Acetylcholine receptor

- Benzodiazepines bind to a specific site on the $GABA_A$ receptor, causing a conformational change, which opens a central pore allowing an influx of Cl^- ions, leading to cell hyperpolarisation.

> **Intermediate (secondary) messengers:**
- There are several types of secondary messengers including cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), inositol triphosphate (IP_3), diacylglycerol (DAG) and calcium ions (Ca^{2+}).
- These are involved in signal transduction and signal amplification, and the rate of production of these second messengers is altered by a ligand binding to a G-protein-coupled receptor (GPCR).
- They have a diverse effect on the cell by activation of protein kinases and modulation of calcium channels.
- cAMP is activated by G_s proteins (e.g. via stimulation of β adrenoceptors and glucagon receptors).
- cAMP is inhibited by G_i proteins (e.g. via stimulation of α_2 adrenoceptors and opioid receptors).
- IP_3 and DAG are activated by G_q proteins (e.g. via stimulation of α_1 adrenoceptors and muscarinic acetylcholine receptors).
- cGMP is activated by nitric oxide.

> **Regulation of gene transcription:**
- These receptors are located intracellularly and are targeted by lipid-soluble ligands, typically hormones (e.g. thyroxine and steroids), that can diffuse easily into the cell.
- Once in the cytosol, the ligands bind with receptors and then the ligand–receptor complex enters the nucleus, alters DNA transcription and therefore protein synthesis.
- This system operates over a matter of hours, which explains why it takes 6–8 hours to achieve a clinical response following hydrocortisone administration in acute asthma.

What is the structure of the G-protein-coupled receptor (GPCR)?

> GPCR consists of seven α helices, which span the cell membrane forming an extracellular site (where the ligand binds) and an intracellular site (where the G protein attaches).

> Each GPCR can be associated with up to a hundred G proteins, which promotes signal amplification.

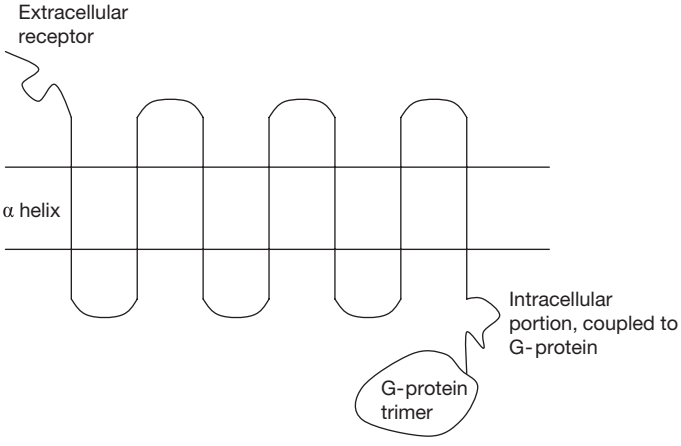


Fig. 1.2 Schematic representation of a G-protein coupled receptor

What are G proteins?

> G proteins (or GTP-binding proteins) are regulatory proteins, which couple the activation of a surface receptor to the activation of an intracellular enzyme (e.g. adenylate cyclase) so that a secondary messenger can be produced (e.g. cAMP), allowing signal transduction and amplification to occur.
> They are heterotrimeric proteins (i.e. they consist of α, β and γ subunits, which join together to form a trimer).

Which different types of G proteins are there?

> The main types of G proteins are the 'stimulatory' (i.e. G_s and G_q) and the 'inhibitory' (i.e. G_i) proteins.
> G_s proteins stimulate adenylate cyclase, causing a rise in cAMP (e.g. β adrenoceptors and glucagon receptor).
> G_q proteins stimulate phospholipase C, causing a rise in IP_3 and DAG (e.g. α_1 adrenoceptor and muscarinic acetylcholine receptor (mAChR)).
> G_i proteins inhibit adenylate cyclase, causing a fall in cAMP (e.g. α_2 adrenoceptors and opioid receptors).

What happens when a GPCR is activated?

> When a ligand binds to the extracellular site of a GPCR, it causes a GTP molecule to bind to the intracellular α subunit of the G-protein trimer.
> This causes a conformational change within the trimer, resulting in its separation from the receptor and dissociation into a βγ and an α-GTP complex.
> The α-GTP complex then goes on to activate (or inhibit) the various enzymes systems (e.g. adenylate cyclase, guanylate cyclase and phospholipase C) resulting in the production of the secondary messengers.
> The α subunit has intrinsic GTPase activity and so it converts the GTP into GDP.
> Once the α subunit is bound only to GDP, it rejoins the βγ units to return to its resting state. The reformed G-protein trimer reattaches to the intracellular portion of the receptor and the receptor system is ready to be stimulated once again.

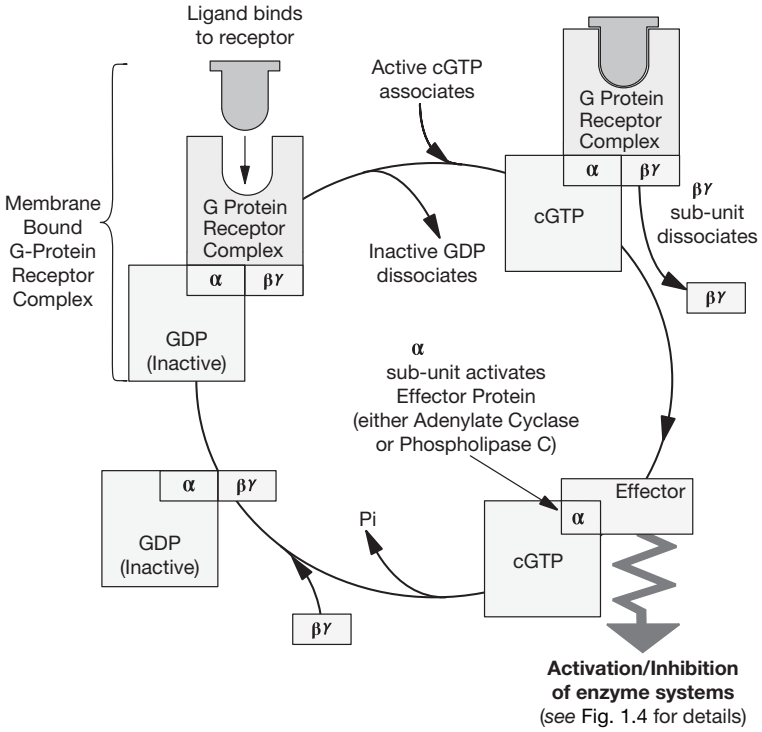


Fig. 1.3 Activation of G-protein coupled receptor

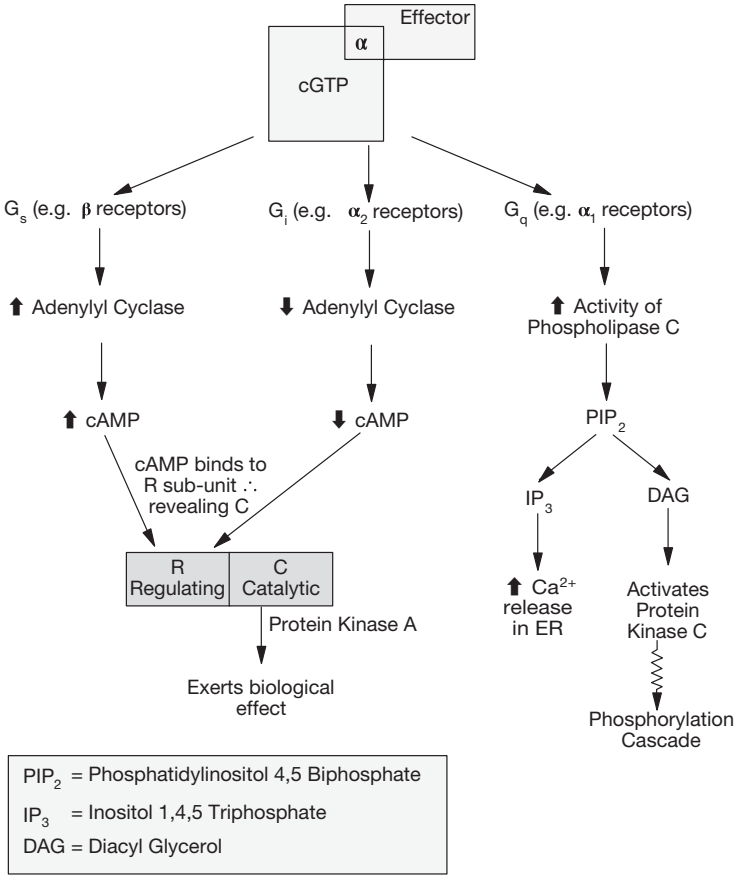


Fig. 1.4 Effects of activating G-protein coupled receptor

2. MECHANISM OF DRUG ACTION

How do drugs work?

Drugs produce their effects by acting on numerous different systems within the body. Below is a list of the effecter sites at which drugs act, along with some clinical examples.

Receptors

> Ligand-gated ion channels
  - Suxamethonium is an agonist at nAChR while rocuronium is an antagonist.
  - Diazepam is an agonist at $GABA_A$ receptors while flumazenil is an antagonist.

> G-protein-coupled receptors
  - Dobutamine is an agonist at β-adrenoceptors while atenolol is an antagonist.
  - Morphine is an agonist at opioid receptors while naloxone is an antagonist.

> Tyrosine kinase receptors
  - Insulin is an agonist at insulin receptors.

> Intracellular receptors
  - Hydrocortisone is an agonist at steroid receptors.

Ion channels

- Lignocaine blocks the fast Na^+ channels.
- Verapamil blocks L-type Ca^{2+} channels.

Enzymes

- Neostigmine inhibits acetylcholinesterase.
- Aspirin inhibits cyclo-oxygenase 1 and 2.

Hormones

- Carbimazole reduces thyroxine production.
- Metformin increases insulin production.

Neurotransmitters

- Ephedrine increases presynaptic noradrenaline release.
- Amitriptyline and cocaine reduce noradrenaline reuptake.

Transport systems

- Digoxin inhibits the cardiac Na^+/K^+ ATPase pump.
- Furosemide inhibits the $Na^+/K^+/2Cl^-$ ATPase pump in the loop of Henle.

Physicochemical

- Sugammadex chelates rocuronium.
- Antacids neutralise gastric acids.

3. DRUG INTERACTIONS

What is a drug interaction?

> A drug interaction occurs when the action of one drug is altered by the concurrent or prior administration of another drug.
> It is estimated that one in six drug charts contains a significant drug interactions. This is becoming increasingly significant as many patients are on multiple drugs, some of which can interfere with anaesthetic agents.

How can drug interactions be classified?

> **Physicochemical** drug interactions occur due to the physical properties of the drugs themselves.
> **Pharmacokinetic** drug interactions occur when one drug alters the way in which the body handles another.
> **Pharmacodynamic** drug interactions occur when the action of one drug is altered by the administration of another.

Give examples of physicochemical drug interactions you may encounter.

Some drug interactions are clinically useful:

> **Chelation**
  - Sugammadex and rocuronium

> **Neutralisation**
  - Heparin and protamine

Others occur inadvertently with undesirable effects:

> **Precipitation**
  - Thiopentone (weak acid) and suxamethonium (weak base)

> **Adsorption**
  - Halothane dissolving into rubber

Give examples of pharmacokinetic drug interactions.

These drug interactions can affect drug absorption, distribution, metabolism and excretion.

> Absorption
  - Adrenaline administered with local anaesthetics reduces absorption of the local anaesthetic by causing local vasoconstriction

> Distribution
  - Aspirin (80% plasma protein bound) displaces warfarin (97% plasma protein bound) from plasma proteins, thereby increasing the unbound fraction of warfarin and increasing the risk of bleeding.

> Metabolism
  - Phenytoin, carbamazepine, rifampicin and barbiturates induce hepatic enzymes, which results in the accelerated breakdown of drugs metabolised by these enzymes.
  - Omeprazole and cimetidine inhibit hepatic enzymes, reducing the breakdown of drugs metabolised by these enzymes.

> Excretion
  - Alkalinising the urine increases the renal excretion of salicylates.

Give examples of pharmacodynamic drug interactions.

> **Summation** occurs when the action of two or more drugs is additive (i.e. 1 + 1 = 2):
  - nitrous oxide and inhalational anaesthetic agents.
> **Synergism** occurs when the combined action of two or more drugs is greater than the sum of their individual effects (i.e. 1 + 1 > 2):
  - propofol and remifentanil
> **Potentiation** occurs when the action of one drug is increased by the administration of another drug:
  - probenecid increases the action of penicillin by reducing its renal excretion
> **Antagonism** occurs when the action of one drug is blocked or reversed by another drug (i.e. 1 + 1 = 0):
  - morphine and naloxone.

4. DRUG ABSORPTION AND BIOAVAILABILITY

What factors influence drug absorption?

Drug absorption describes the passage of a drug into the bloodstream from its route of administration. Factors influencing this are as follows:

> **Route of administration**
> **Particle size**
> **pK_a and ionisation:** Unionised drugs cross membranes more readily (*see* below).
> **Lipid solubility:** The more lipid soluble a drug, the more readily it can cross the phospholipid bilayer of cells, and the faster it is absorbed.
> **Concentration gradient:** The higher the concentration gradient between the lumen containing the 'drug load' and the cells into which it is diffusing, the faster it will be absorbed.
> **Other factors:** Bacterial overgrowth will reduce drug absorption and some drugs will be affected by intake of other substances, e.g. milk chelates tetracycline antibiotics and so decreases their availability for absorption.

How can manufacturers alter rate of drug absorption?

Most drugs are taken orally and pass from the mouth into the aqueous and acidic environment of the stomach. Here they may dissolve and cross into the cells lining the stomach. Dissolution and absorption can be altered by the manufacturers in several ways:

> **Particle size:** The larger the particle size (molecular weight) of the drug, the more slowly it will dissolve.
> **Compounds used:** Different compounds dissolve at different rates. Modified-release or slow-release drugs can improve the drug profile, minimising peaks and troughs in plasma concentration. Patient compliance improves with less frequent dosing.
> **Coating the tablet:** Enteric coating does not dissolve in acid conditions and therefore the drug will pass to the basic intestine before dissolving.

What are the available routes for drug administration?

> Enteral (variable availability: formulation of drug, pK_a, gastric pH, GI transit time, etc.)
> Intravenous (bioavailability is taken as 1.0 or 100%)
> Transdermal (suitable for small, potent, lipophilic drugs)
> Intranasal (rich blood supply, avoids first-pass metabolism, variable absorption: mucus flow etc.)
> Sublingual (rich blood supply, avoids first-pass metabolism, variable absorption: saliva flow, swallowing etc.)
> Intrapulmonary (conduit for volatile agents to lungs: large surface area, rich blood supply)
> Intramuscular (variable absorption: regional blood flow, injections can be formulated for slow release)

- Epidural (reduced systemic absorption in general, localised effect though beware, opioids may still cause respiratory depression)
- Subarachnoid (as above)
- Rectal (avoids first-pass metabolism, useful when nausea and vomiting problematic)
- Vaginal (avoids first-pass metabolism, limited systemic absorption, primarily used to administer drugs whose action is on vagina/nearby structures)

What is pK_a and how does this influence drug absorption?

Before answering this question, a reminder of some basic concepts:

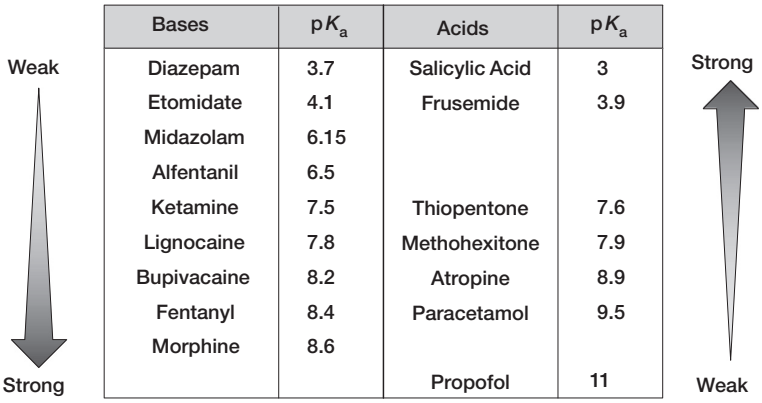
- An **acid** is a proton (H^+ ion) donor.
- A **base** is a proton acceptor (OH^-).
- A **weak acid/base** is one that dissociates in water to form an equilibrium with its ions, e.g. $H_2CO_3 \rightleftharpoons H^+ \rightleftharpoons HCO_3^-$.
- A **strong acid/base** is one that dissociates very readily and does not form an equilibrium, e.g. $HCl \rightarrow H^+ + Cl^-$.
- An amphoteric compound has the ability to behave as an acid or a base, e.g. water (in some senses, all compounds are amphoteric as they can always be (de)protonated by a stronger acid/base).
- The K_a is the dissociation constant and it describes how readily an acid in solution gives up its hydrogen ions.
- It describes the ratio of the products of the reaction, to the concentration of the initial reactants.
- It is written:

$$\mathbf{K_a = \frac{[A^-][H^+]}{[HA]}}$$

where HA is the acid, A^- is its conjugate base (i.e. the product that is now able to accept protons) and H^+ its proton. The higher the value of K_a, the more readily the acid gives up its proton and dissociates.

- K_a can be expressed in its logarithmic form giving us the pK_a.
- pK_a is the negative log of the acid dissociation constant, and is defined as $-\log_{10} K_a$.
- pK_a is used because it yields more convenient units that are easier to use for practical purposes.
- The pK_a of a drug is the pH at which it is exactly half dissociated, i.e. the drug is 50% ionised and 50% unionised.
- The larger the value of pK_a, the less readily the acid dissociates to donate its H^+ ion at a given pH, i.e. the weaker the acid. Conversely, the smaller the value of pK_a, the more readily the acid donates its proton and the stronger the acid.

> *Most drugs are either weak acids or weak bases. Unfortunately, you cannot tell from the pK_a of a drug whether it is basic or acidic; this is a property of each drug you just have to learn.*



Bases	pK_a	Acids	pK_a
Diazepam	3.7	Salicylic Acid	3
Etomidate	4.1	Frusemide	3.9
Midazolam	6.15		
Alfentanil	6.5		
Ketamine	7.5	Thiopentone	7.6
Lignocaine	7.8	Methohexitone	7.9
Bupivacaine	8.2	Atropine	8.9
Fentanyl	8.4	Paracetamol	9.5
Morphine	8.6		
		Propofol	11

Fig. 4.1 pK_a values of some basic and acidic drugs

At pH < pK_a, acidic drugs become less ionised:

$$HA \rightleftharpoons H^+ + A^-$$

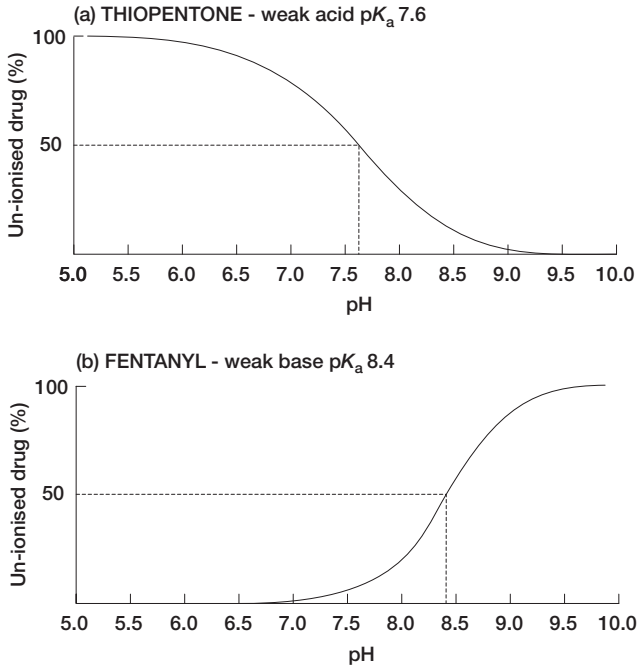
Putting the acidic drug in a more acidic environment raises H^+ concentration and so drives the equation to the left.

At pH < pK_a, basic drugs become more ionised as they accept protons:

$$B + H^+ \rightleftharpoons BH^+$$

Putting a basic drug in an acidic environment drives the equation to the right as the base (B) 'accepts' the protons.

Drugs cross membranes in the un-ionised state and so their pK_a and the pH of the surrounding environment affect their rate of absorption. Hence, acidic drugs will be more readily absorbed in the highly acidic stomach, whereas basic drugs are better absorbed in the intestine where pH is higher.



Relationship between pH and the percentage of drug in the un-ionised form, for (a) a weak acid (thiopentone: pK_a 7.6) and (b) a weak base (fentanyl: pK_a 8.4)

Fig. 4.2 pH vs. degree of ionisation for thiopentone and fentanyl

What is the Henderson–Hasselbalch equation and how is it useful in predicting drug absorption?

> The Henderson–Hasselbalch equation describes the derivation of pH as a measure of acidity. pH is calculated using the pK_a and the equation can be expressed in two ways:

$$pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{acid}]}$$

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Where pK_a is –log (K_a).

> Using the non-specific acid–base reaction: $HA + H_2O \rightleftharpoons A^- + H_3O^+$ pK_a can be substituted into the equation, to give the Henderson–Hasselbalch equation:

$$-\log(K_a) = -\log \frac{[H_3O^+][A^-]}{HA}$$

> This is used to calculate:
- pH of a solution
- pH at which the equation is in equilibrium and the drug exists as 50% ionised and unionised, i.e. the pK_a of the drug, proportions of ionised and un-ionised drug in a solution at a given pH.

Define bioavailability.

> Bioavailability describes the fraction of the drug administered that reaches the bloodstream.
> If a drug is given intravenously it is introduced straight into the bloodstream and is said to have a bioavailability of 1 or 100%.
> For drugs given orally, the bioavailability is calculated by comparing the plasma concentration of the drug when administered orally to the plasma concentration when it is administered intravenously. This is achieved by comparing the area under the curve (AUC) of the two conditions:

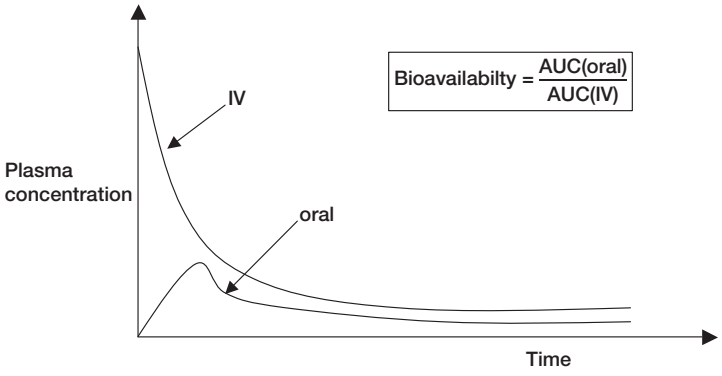


Fig. 4.3 Plasma concentrations of a drug administered intravenously and orally

What is first-pass metabolism?

> This refers to the process by which drugs absorbed from the gastrointestinal tract enter the hepatic portal circulation and are carried to the liver. The liver then metabolises the drug such that only a fraction of the original dose is returned to the systemic circulation.
> Drugs that undergo extensive first-pass metabolism have low oral bioavailability and it may be necessary to find an alternative route of administration that allows the drug to enter the systemic circulation directly.

Can you give examples of drugs that undergo first-pass metabolism?

> Aspirin (70%)
> Codeine (60%)
> Morphine (40%)
> Diltiazem (40%)
> Propranolol (30%)
> Verapamil (20%)
> Hydralazine (15–30%)

5. DRUGS AND THE LIVER

In which ways are drugs metabolised by the liver?

The metabolism of drugs in the liver is defined as the modification or degradation of drugs in order to activate, deactivate, toxify or detoxify drugs in the body.

The majority of metabolic reactions serve to de-activate and aid the excretion of the drugs, often by turning a lipophilic compound to a readily excreted polar one (*see* Chapter 6: 'Drugs and the kidney').

The rate at which the drug is metabolised will be an important factor in the intensity and duration of the drug's action.

Some drugs are given as pro-drugs that need to be metabolised in order to become active, e.g. enalapril, which must be converted to enalaprilat for its action. Others may have active substrates, such as morphine, or substrates with completely different actions.

How are drugs metabolised by the liver?

The types of reaction that occur can be classified into phase I or phase II reactions. While they may occur in other parts of the body, the majority take place in the smooth endoplasmic reticulum of liver.

Phase I reactions:

- These normally precede phase II reactions and involve oxidation, reduction or hydrolysis of the drug in order to activate or deactivate it.
- The reaction usually adds or unmasks polar bodies in the chemical.
- Oxidation and reduction are mainly hepatic, whereas hydrolysis is more widespread throughout the body, e.g. by plasma cholinesterase.
- For oxidation reactions the cytochrome P450 system of enzymes is particularly important. These enzymes show genetic variability and their activity can be induced or inhibited by the presence of certain other drugs or chemicals (*see* Table 5.1). This becomes of particular importance when the drugs concerned have a narrow therapeutic window and inhibition of their metabolism will cause toxicity, or induction of their metabolism will render them ineffective.
- Drugs undergoing phase 1 reactions include phenothiazines, paracetamol and steroids.
- For some drugs, this reaction will be sufficient to allow excretion, but others will require further modification and undergo phase II reactions.

Table 5.1 List of common drugs that induce or inhibit the hepatic cytochrome P450 enzyme system

Inhibitors	Inducers
Metronidazole	Carbamazepine
Ciprofloxacin	Rifampicin
Fluconazole	Alcohol (Acute intake)
Erythromycin	Phenytoin
Ethanol (Chronic use)	Griseofulvin
Dextroproxyphene (co-proxamol)	Primidone
Cimetidine	Inhalational agents (enflurane, halothane)
Amiodarone	Smoking
Ketoconazole	Barbiturates
Etomidate	Glucocorticoids
Grapefruit	

Phase II reactions:

> These involve adding groups to the drugs and are sometimes referred to as conjugation or synthetic reactions. These groups increase the water solubility of the drugs and allow excretion in the bile or urine. Although they often follow Phase I reactions they may be the only step in the metabolism of drugs.
> Phase II reactions include glucuronidation, sulphation, acetylation and methylation.

Which drugs can cause damage to the liver?

Drug-induced hepatitis can follow acute or chronic drug exposure. The most commonly encountered drug causing direct hepatocellular damage is ethanol. Chronic alcohol abuse in genetically susceptible individuals can cause progressive inflammatory liver damage, which may result in fatty liver and cirrhosis.
Alcohol damages the liver in several ways:

> Ethanol and its metabolite acetaldehyde damage the liver cell and mitochondrial membranes.
> Free radicals, superoxides and hydroperoxides generated during ethanol metabolism damage the liver.
> Alcoholic hepatitis stimulates the immune system, which generates autoantibodies.

The volatile anaesthetic agent halothane is also known to cause hepatitis, with a mortality rate of 50% in those affected.

> Halothane can cause a reversible transaminitis as a result of hepatic hypoxia.
> It can cause significant centrilobular liver necrosis in what appears to be an immune-mediated process.
> Halothane is oxidised, producing trifluroacetyl metabolites, which bind to liver proteins. In genetically susceptible individuals this causes an autoimmune response and antibodies are generated against the complex.
> Risk factors include repeated exposure, female sex, obesity and middle age.

The volatile agents enflurane and isoflurane are also metabolised to acetylated metabolites, but this only involves 2 and 0.2% of the total dose respectively, compared to 20% of halothane.

How does chronic liver disease affect the drugs used in anaesthesia?

- Porto-caval shunts occurring in cirrhosis reduce hepatic blood flow and hence the extraction ratio of the drug. This results in an increased drug bioavailability.
- Impaired production of albumin results in reduced drug plasma protein binding. This leads to an increase in the free, active component of the drug.
- Ascites and the overall increase in total body water leads to an increase in the volume of distribution of drugs.
- Reduced metabolic function (phase I and II reactions) leads to prolonged action of hepatically metabolised drugs.
- Impaired coagulation (the liver synthesises many of the clotting factors) and liver-induced thrombocytopenia may contraindicate the use of central neuroaxial blocks.

Benzodiazepines:	Metabolism impaired and effects enhanced. These drugs should be avoided.
Opiates:	Metabolism impaired and effects enhanced. Use with caution in reduced doses.
Barbiturates:	Metabolism impaired, though their effects are terminated by redistribution.
Suxamethonium:	Duration of action prolonged as decreased plasma cholinesterases.
Muscle relaxants:	Effects enhanced as usually highly protein bound.
	Hoffmann degradation of atracurium may be reduced in the lower pH associated with severe disease.
Fluid:	Extreme care should be used in administering intravenous fluids as oedema and fluid overload are likely. Also avoid lactate-containing fluids, e.g. Hartmann's as lactate metabolism will be impaired.

6. DRUGS AND THE KIDNEY

How are drugs excreted from the body?

> Most drugs are excreted from the body by a combination of metabolism by the liver and excretion via the kidneys.
> Most parent drug molecules and their phase I metabolites are extensively reabsorbed at the level of the kidney tubules, whereas their more water-soluble phase II conjugates are only minimally reabsorbed and readily excreted.
> Some parent drugs are almost exclusively excreted by the kidneys without prior detoxification, such that any alteration in kidney function can result in toxicity. Examples include:
  - Oxybarbiturates
  - Gentamicin
  - Furosemide
  - Ampicillin
  - Sotalol
  - Methotrexate.

Describe how drugs are handled as they pass through the kidney, illustrating your answer with examples.

The kidney affects drug elimination at three main stages:

> Glomerular filtration
> Active proximal tubular secretion
> Passive distal tubular reabsorption

Glomerular filtration

> The rate of filtration is governed by the glomerular filtration rate.
> Drugs that are of low molecular weight (<60 000 Daltons) and that are not plasma protein bound (PPB) are readily filtered, e.g. fluconazole and ofloxacin.
> Most intravenous anaesthetic agents are of low molecular weight but are highly protein bound, e.g. propofol (98% PPB).
> Heparin is a large molecule that cannot be filtered.

Active proximal tubular secretion

> The rate of tubular secretion is governed by renal blood flow.
> It is an energy-dependent process and is carrier mediated.
> Two types of carrier exist:
  - Those for acidic drugs, e.g. furosemide, penicillin, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucuronide and sulphate conjugates
  - Those for basic drugs, e.g. histamine and dopamine
> Tubular secretion is more important for acidic rather than basic drugs.
> Many drugs are actively secreted from the renal blood vessels into the proximal tubules because most of the renal blood flow (80%) escapes filtration by the glomeruli, e.g. angiotensin-converting enzyme (ACE) inhibitors and penicillin.
> Some drugs compete for the same carriers and limit the other's secretion, e.g. probenecid administered with penicillin and sulphonamides administered with indomethacin.
> Tubular secretion can secrete drugs against their concentration gradients. It is an efficient system even for highly protein-bound drugs.

Passive distal tubular reabsorption

> As water is reabsorbed along the tubule, the drug's increasing concentration gradient drives the process of passive reabsorption.
> Highly lipid-soluble drugs, e.g. fentanyl, are reabsorbed into the circulation as they pass down the distal convoluted tubule.
> Some drugs are too lipid insoluble to undergo reabsorption, e.g. digoxin, aminoglycoside antibiotics, and glucuronide and sulphate conjugates from phase II metabolism.
> Changes in urine pH can alter the tubular reabsorption of weakly acidic or basic drugs by altering their degree of ionisation and consequently their lipid solubility. This, in turn, affects their speed of elimination.
> Weak bases become more ionised (lipid insoluble) in acidic urine and therefore less well reabsorbed.
> Weak acids become more ionised in alkaline urine. This is applied clinically in the administration of sodium bicarbonate to alkalinise the urine in overdoses of aspirin and phenobarbital.

What are the effects of age on renal drug metabolism?

Renal function, notably GFR decreases with age.

> Increasing age is associated with progressive loss of kidney structure and function with decreases in glomerular filtration rate (GFR) and renal blood flow (RBF).
> Consequently, drug elimination is reduced, and the elderly are at increased risk of acute renal failure in the post-operative period.
> GFR (140 ml/min/1.73 m^2 in adulthood) and thus creatinine clearance declines by about 8 ml/min/1.73 m^2 per decade after the age of 40.
> Serum creatinine remains within the normal range because although less is excreted, less creatinine is also produced (less muscle mass and less physical activity).
> RBF is well maintained at 500–600 ml/min until the fourth decade, and then declines by about 10% per decade.

Both structural and haemodynamic changes are responsible.

> Haemodynamic changes:
  - Reduced glomerular capillary plasma flow rate
  - Reduced glomerular capillary ultrafiltration coefficient (due to reductions in both the glomerular capillary permeability and the surface area available for filtration)
  - Reduction in afferent arteriolar resistance, with an increase in glomerular capillary hydraulic pressure, and accompanying proteinuria and progressive glomerular sclerosis.

> Structural changes:
  - Reduced renal mass, in particular the cortex (adult kidney 400 g, declines by eighth decade to 300 g)
  - Reduced number of glomeruli (absolute and functional)
  - Hyalinisation of afferent arterioles
  - Development of aglomerular arterioles (direct channels between the afferent and efferent arterioles)
  - Increased percentage of sclerotic glomeruli (5% by 30 years; 30% by 80 years)
  - Tubulointerstitial fibrosis.

In addition, ageing is associated with other systemic changes that contribute to reductions in RBF and GFR:

> Altered cardiovascular haemodynamics (reduced cardiac output and increased systemic blood pressure)
> Altered responsiveness to vasoactive stimuli (vasoconstrictor responses are enhanced, while vasodilatory responses are impaired).

Examples of drugs where elimination may be significantly affected
The above changes decrease renal elimination of many drugs and doses or their frequency needs adjusting:

- Analgesics: morphine, remifentanil, oxycodone, gabapentin
- Neuromuscular blocking agents: aminosteroid group (vecuronium > rocuronium > pancuronium)
- Neuromuscular blocking agent antagonists: neostigmine and sugammadex
- Cardiovascular drugs: ACE inhibitors, digoxin
- Diuretics: furosemide, thiazides, amiloride
- Antibiotics: amikacin, gentamicin, ciprofloxacin, levofloxacin, streptomycin.

Most other anaesthetic agents and adjuvant drugs require dose adjustments in the elderly for reasons other than reduced renal elimination.

7. VARIATIONS IN DRUG METABOLISM

What factors can cause a variable biological response to drugs amongst patients?

There are several factors that affect drug handling in different patient groups, for example:

> Age, e.g. elderly patients are often volume deplete and so volume of distribution of drug may be decreased.
> Race, e.g. there is evidence that ACE inhibitors are less effective at treating heart failure in black patients than in white.
> Sex, e.g. men have higher levels of alcohol dehydrogenase than women
> Disease state, e.g. in liver disease decreased production of plasma. proteins may alter drug binding; cancer, obesity, heart failure and infection among other things can alter the activity of drug-metabolising enzymes.
> Genetic polymorphism – *see* below.

Explain how genetic polymorphism influences drug metabolism. What clinical effects can this have?

This question is a clear lead into a discussion about suxamethonium apnoea, but do not forget about other drugs whose actions are also affected by the recipient's genetics.

Genetic polymorphism is a term that describes the difference in people's genotype and subsequent variation in phenotypic expression of these genes. The enzymes that metabolise drugs are subject to genetic polymorphism, and so there can be differences between individuals in the handling of the same drug.

> **Suxamethonium:**
- Suxamethonium is broken down by plasma cholinesterases.
- These enzymes are coded for by autosomal genes on chromosome 3. The normal phenotype is Eu (usual). A patient with Eu:Eu will break down suxamethonium rapidly so that its duration of action is around 2–6 minutes.
- There are several variations of these genes and deviation from the normal means that the resulting enzyme's activity is decreased. Consequently, it takes longer to break down the suxamethonium and its duration of action is increased.
- Abnormal forms of the gene include Ea (atypical), Es (silent) and Ef (fluoride resistant).
- The most common abnormality is Ea:Eu. This is carried by 4% of the Caucasian population, and their recovery time following suxamethonium is extended to around 30 minutes. The incidence of this phenotype is higher in Asians and lower in Afro-Caribbeans.

Incidence and prolongation of block:

Ea:Ea	1/3000	≥2 hours
Ef: Ef	1/100 000	≥3 hours
Es:Es	1/250 000	≥3 hours