Chapter 1

General principles of pharmacology

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Basic principles

A drug is a molecule or particle that produces a therapeutic effect by modifying how a biological system responds to a physical or chemical stimulus. This effect can occur locally at the site of administration or after absorption and delivery to a more distant site of action through carriers or mass transit. Most drugs undergo passive or active transport across membranes as part of this process. Drugs may be organic or inorganic and of peptide or non-peptide origin. Organic molecules have a carbon skeleton, with functional classification dependent on the associated functional groups (giving rise to compounds such as esters and amines). Inorganic molecules arise from non–carbon-based structures. Examples of inorganic substances used as drugs include salts of lithium and magnesium. Chemical structure and other characteristics influence the effects of drugs on the body (pharmacodynamics) and the handling of the drug by the body (pharmacokinetics).

The activity of a drug is determined by its ability to interact with its target; these interactions may be selective or non-selective. The former describes interaction with a single type of receptor (e.g. atenolol is cardioselective as it has greater effects on the β_1 myocardial adrenoceptors than the β_2 bronchial adrenoceptors). Selective drug interactions with receptors and enzymes occur because a specific region on the ligand fits a complementary region on the effector molecule. This lock and key mechanism is critical to the functioning of some drugs. Some interactions occur without the recognition of a molecular structure or motif. These non-specific interactions are known as physicochemical effects and include neutralisation of stomach acid by antacids, or molecular adsorption onto activated charcoal.

The interaction and transportation of drugs within the body is determined by factors specific to both the drug and the patient. Drug-related factors include the nature of the drug itself, chemical structure, size, lipid and water solubility, ionisation and charge. Patient-related factors influencing drug uptake and subsequent effects include regional blood flow, barriers to uptake such as membranes, the presence of specific transport or acceptor molecules and the presence of other modifying drugs or hormones.

Chemical structure

Organic molecules consist of functional groups organised around a carbon skeleton. These structures may adopt different conformations allowing specific and non-specific interactions with receptors and binding with proteins and other molecules within the body. The physical organisation of the drug's molecules, functional groups and charge determines further interactions between groups on the same or other molecules. The exposure of charges and hydrophobic or hydrophilic groups may influence a drug's ability to cross membranes, reach a site of action or be excreted.

Isomerism

Isomers are molecules sharing the same chemical formula but with a differing physical arrangement of atoms. Different forms (enantiomers) may interact with other molecules in a variable way and this, therefore affects function. There are several different classes of isomer (Fig. 1.1).

Structural isomerism describes the organisation of functional groups within an organic molecule, where either the carbon skeleton, functional group or position of functional groups along a chain differs. Isoflurane and enflurane share the formula $C_3H_2ClF_5O$ but have differences in solubility, metabolism, potency (as defined by the minimum alveolar concentration, or MAC) and other characteristics. The different positions of the highlighted F and Cl atoms in

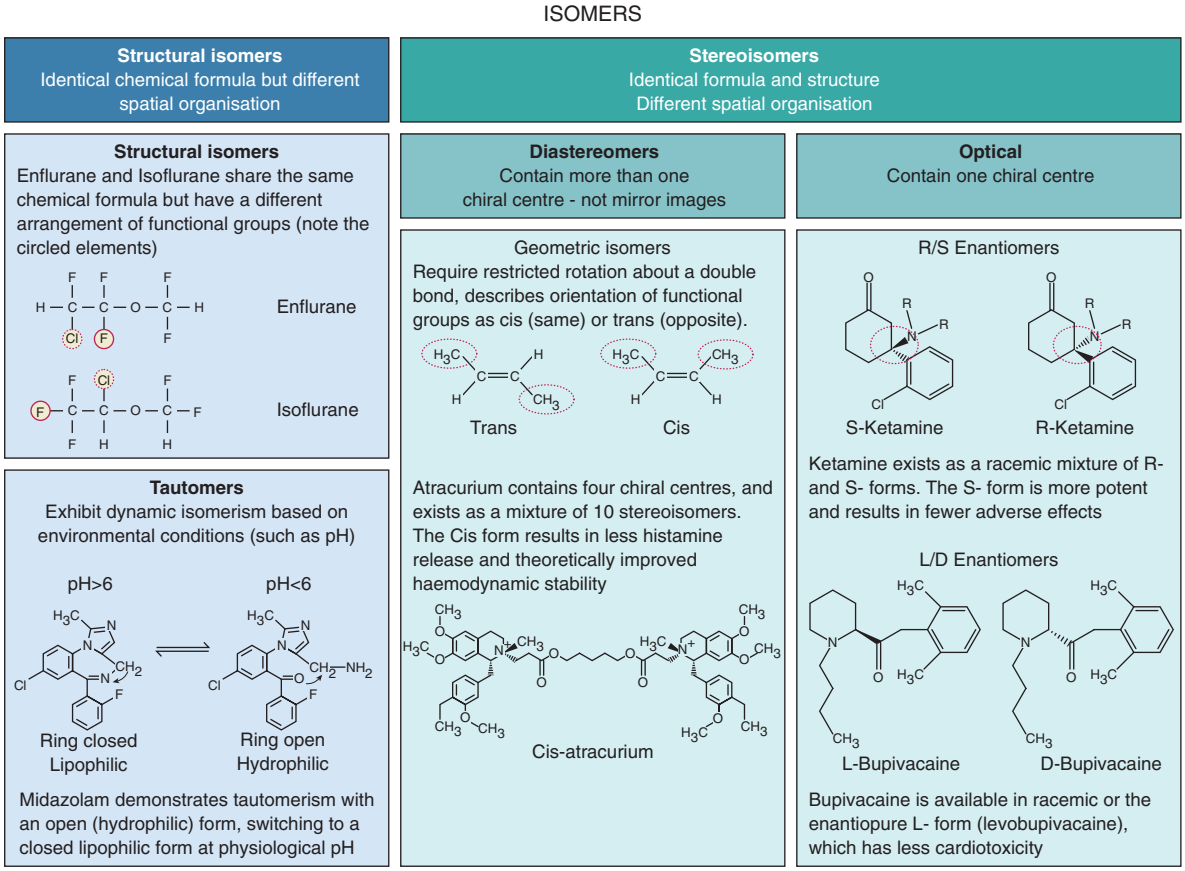

Fig. 1.1 Classification of isomers with examples from anaesthetic practice.

Fig. 1.1 distinguish these different isomers. Because of the molecular size, spatial conformation and charges contained within these functional groups, the different configurations can affect end function and particularly interaction with receptors and target molecules.

Stereoisomerism refers to molecules with identical chemical and molecular structures but a different spatial organisation of groups around a chiral atom (usually carbon). Chiral atoms are present in all stereoisomers and have bonds entirely occupied by dissimilar functional groups. Stereoisomers are subclassified by the direction in which they rotate plane polarised light (optical isomerism) and/or by the spatial arrangement of atomic groups around the chiral centre. When polarised light is travelling towards the viewer, it can be rotated clockwise (termed dextrorotatory (*d*) or +) or anticlockwise (laevorotatory (*l*) or −). The *dextro* (+) and *laevo* (−) enantiomers of a compound are non-superimposable geometric mirror images of each other. The alternative R/S classification organises compounds according to the atomic number of groups of atoms attached directly to the chiral centre. When viewed with the lowest priority (lowest atomic number) facing away, the priority of the other groups can decrease clockwise (R form) or anticlockwise (S form). These correspond to 'right-handed' (rectus) or 'left-handed' (sinister) forms. Note that the *laevo*/*dextro* (or +/−) and R/S properties of a drug are independent.

The different configurations are known as enantiomers. Naturally occurring compounds (including some drugs) contain R and S forms in equal proportions – a *racemic mixture*. However, as enantiomers may have different properties (including receptor binding, activity and effects) it may be advantageous to use an enantiopure drug formulation that contains a single enantiomer. Examples include S(+) ketamine and levobupivacaine, as discussed later.

Molecules containing more than one chiral centre are described as *diastereomers*, which may form geometric isomers, based on the orientation of functional groups around a non-rotational carbon-carbon double bond. Fig. 1.1 shows the example of cis- and trans-geometric isomers. Atracurium contains four chiral centres, resulting in 10 stereoisomers present in solution. The enantiopure form, cisatracurium, causes less histamine release than the non-pure form, theoretically conferring greater haemodynamic stability.

Tautomerism describes dynamic structural isomerism, where drug structure may change according to the surrounding environment. For example, midazolam has an open, water-soluble ring structure in storage at pH 3 but undergoes a conformational change at body pH of 7.4 to become a completed ring structure, which is lipid soluble and passes through the blood–brain barrier.

Ketamine

Ketamine is a phencyclidine derivative used for analgesia and sedation. It has a chiral centre, forming R and S enantiomers that exhibit (+) and (−) optical stereoisomerism (see Fig. 1.1).

In its usual formulation as a racemic mixture of the R(−) and S(+) forms, ketamine produces dissociative amnesia and analgesia but with significant tachycardia, hypertension and hallucinations. The S(+) enantiomer is more potent, with a greater affinity at its target N-methyl-D-aspartate (NMDA) receptor, requiring a lower dose for equivalent effect compared with the racemic mixture; this results in fewer adverse effects and a more rapid recovery.

Bupivacaine

Bupivacaine is a local anaesthetic containing a chiral centre and adopts *dextro* and *laevo* forms. The enantiopure *l* form is less cardio- and neurotoxic and has an equivalent potency to the racemic mixture; therefore levobupivacaine is often preferred to reduce the potential for toxicity.

Stereoselectivity describes the differences in response at a given receptor for the different enantiomers (such as the response discussed for S(+) ketamine). The opioid and NMDA receptors also exhibit stereoselectivity.

Transport of drugs

Most drugs must pass from their site of administration to their site of action (effect site) before metabolism and elimination, usually via the kidneys or liver. This occurs by local diffusion across plasma membranes, and subsequently mass transport in the blood through dissolution or carriage by transport proteins.

Transmembrane movement is either active or passive. The former is undertaken by transporter proteins with the hydrolysis of adenosine triphosphate (ATP) or movement of other molecules, and the latter occurs by diffusion with no net utilisation of energy. Facilitated diffusion utilises carrier proteins within the cell membranes to increase diffusion along a concentration gradient.

The rate of passive diffusion is determined by the nature of the drug, barriers or membranes, concentration gradient and temperature. The presence of any transporter molecules or ion channels enhance diffusion. The rate of diffusion is inversely proportional to the square of the molecular weight (Graham's law). The relationship between rate of diffusion and concentration gradient, membrane permeability, thickness and surface area is described by Fick's law. Drug solubility, by virtue of size, charge, and the presence of hydrophilic or lipophilic groups, also determines ease of movement across membranes.

Active transport describes the expenditure of energy to facilitate the movement of molecules, for example via symports, antiports or cotransporters, either at the expense of other molecules or ATP. Bacteria may develop antibiotic resistance by actively extruding antibiotic molecules from their cells via such mechanisms.

Ionisation and equilibria

An acid is a proton donor and a base is a proton acceptor; many drugs are weak acids or bases, partially dissociating to exist in equilibria between ionised and unionised forms. Strong acids and bases are substances that dissociate completely.

The relative proportions of ionised and unionised forms for a given drug may be derived from the Henderson–Hasselbalch equation (Eq. 1.1) and depend on the environmental pH and the p*K*a, the pH at which a given drug exists as equal proportions of its ionised and unionised forms. The p*K*a is determined by the chemical nature of a drug and is independent of whether it is acidic or basic.

Only the unionised forms of a drug or molecule are highly lipid soluble and can cross cell membranes easily, so the environmental pH determines the action of many drugs.

The Henderson–Hasselbalch equation (see Eq. 1.1) can be rearranged to derive the relative proportion of ionised and unionised forms of a drug, given a known p*K*a and pH.

$$\mathrm{pH} = \mathrm{p}K\mathrm{a} + \log_{10}\left(\frac{[\textit{proton acceptor}]}{[\textit{proton donor}]}\right) \qquad \text{(Eq. 1.1)}$$

For a weakly acidic drug dissociating to H^+ and A^-, substituting these into Eq. 1.1 (Eq. 1.2) and rearranging gives the relative proportions of the ionised, A^-, and unionised form, HA (Eq. 1.2C). Similarly for a base, accepting a proton to form BH^+, the same principles apply.

$$\mathrm{pH} = \mathrm{p}Ka + \log_{10}\left(\frac{[\textit{proton acceptor}]}{[\textit{proton donor}]}\right)$$

For an acidic substance

$$\mathrm{HA} \rightleftharpoons \mathrm{H^+} + \mathrm{A^-} \qquad \text{(Eq. 1.2A)}$$

$$\downarrow$$

$$\mathrm{pH} = \mathrm{p}Ka + \log_{10}\left(\frac{[\mathrm{A^-}]}{[\mathrm{HA}]}\right) \qquad \text{(Eq. 1.2B)}$$

$$\downarrow$$

$$10^{\mathrm{pH}-\mathrm{p}Ka} = \frac{[\mathrm{A^-}]}{[\mathrm{HA}]} \qquad \text{(Eq. 1.2C)}$$

For a basic substance

$$\mathrm{B} + \mathrm{H^+} \rightleftharpoons \mathrm{BH^+} \qquad \text{(Eq. 1.2A)}$$

$$\downarrow$$

$$\mathrm{pH} = \mathrm{p}Ka + \log_{10}\left(\frac{[\mathrm{B}]}{[\mathrm{BH^+}]}\right) \qquad \text{(Eq. 1.2B)}$$

$$\downarrow$$

$$10^{\mathrm{pH}-\mathrm{p}Ka} = \frac{[\mathrm{B}]}{[\mathrm{BH^+}]} \qquad \text{(Eq. 1.2C)}$$

(Eq. 1.2)

The equilibria given are dynamic and follow the law of mass action depending on the prevailing [H^+]. The p*K*a is the negative logarithm to the base 10 of the dissociation constant. It is an intrinsic property of a drug or molecule and is also the pH at which half of all molecules are ionised. The ionised (BH^+) form of a weak base predominates at a pH lower than its p*K*a, whereas the converse is true for weak acids. The principles of this are shown in Fig. 1.2.

Local anaesthetics are weak bases (i.e. proton acceptors) with p*K*a values of approximately 8. Therefore at physiological pH (7.4) the environment is relatively acidic compared with the drug, and this renders local anaesthetics ionised. The addition of alkali favours the unionised form (by mass effect) and aids passage of local anaesthetic molecules across the neuronal membrane. Once inside the neuronal tissue, the molecule then becomes charged inside the nerve and is trapped, facilitating interaction with its target, the sodium channel. Acidic environments (in infected tissue) promote the ionised form, preventing entry into nerve tissues, rendering local anaesthetics less effective.

Weak acids, such as thiopental, have the opposite relationship, with the proportion of unionised molecules decreasing with increasing pH (see Fig. 1.2A).

Urinary alkalinisation traps the ionised form of acidic compounds in the renal tubules, preventing reabsorption, and is hence sometimes used in the management of poisoning (e.g. by salicylic acid).

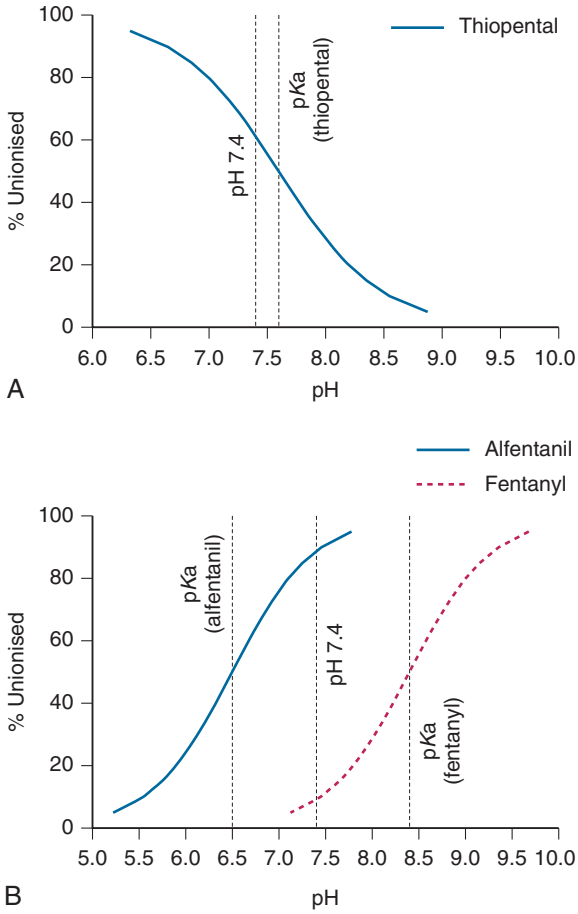

Fig. 1.2 Effect of pH on ionisation for weakly acidic (A) and basic (B) substances.

How do drugs act?

Drugs may act at one or more specific molecules, such as a receptor, enzyme or carrier, or at non-specific sites, for example acid neutralisation by sodium citrate.

Fig. 1.3 and Table 1.1 summarise these intra- and extracellular mechanisms of drug action.

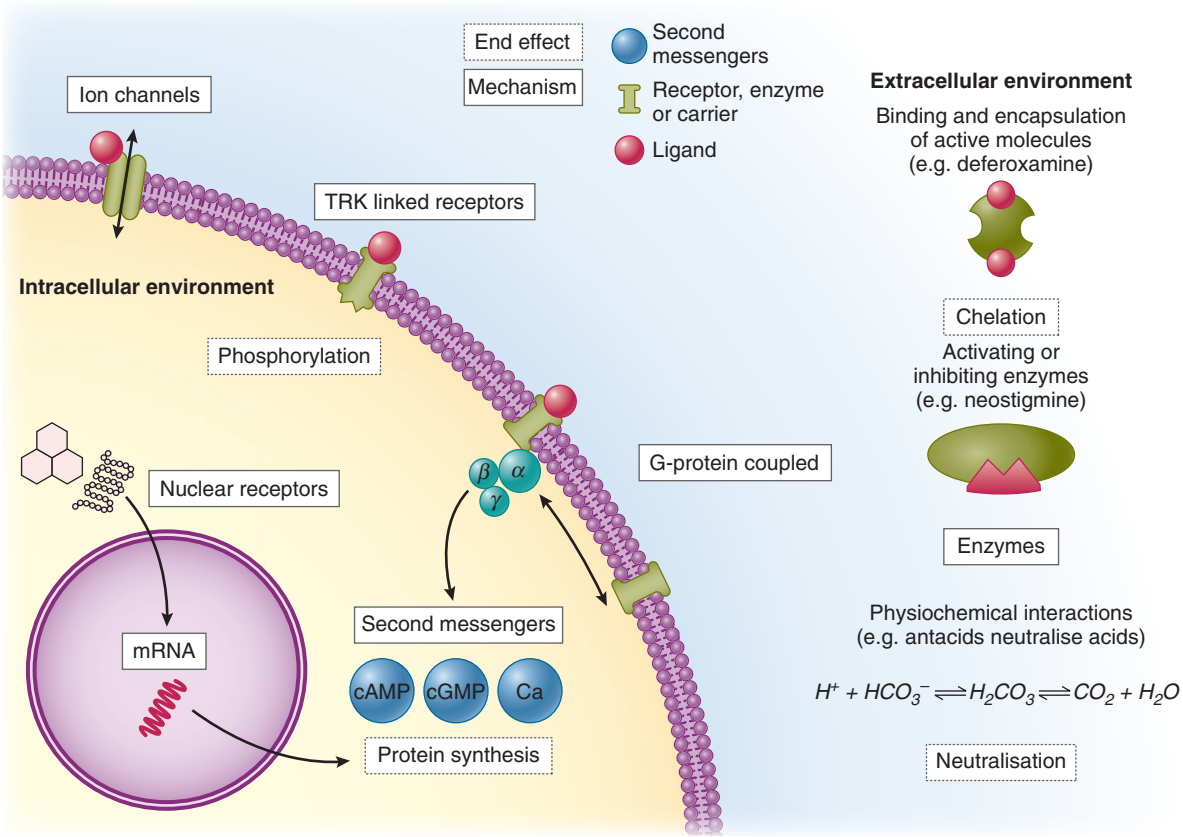

Fig. 1.3 Major targets *(solid boxes)* and mechanisms *(dashed boxes)* of drug action, intra- or extracellular and resulting biochemical changes and second messenger cascades. Targets include channels, carriers and receptors. *mRNA,* Messenger RNA; *TRK,* tyrosine kinase–linked receptors.

The extracellular environment may be affected by chelation, enzymatic breakdown of components or the neutralisation of substances. Receptors are a mechanism for transducing extracellular signals to produce an intracellular response, either via molecules on the cell surface or in the nucleus.

Receptor-mediated effects

Most drugs act at specific receptors. A receptor is a protein that produces an intracellular response when a ligand (which may be a drug or an endogenous molecule) binds to it. In the unbound state, receptors are functionally silent. Increasing knowledge of the molecular structure of the binding regions of receptors and the complementary region on drug molecules facilitates the design of specific, targeted drugs and opens the possibility of reverse pharmacology – the discovery of new ligands for a given receptor structure.

Receptors enable cells to adapt to environmental conditions outside (in the case of membrane-bound receptors) or inside (in the case of nuclear receptors). Receptors may initiate responses locally (such as the opening or closure of ligand-gated ion channels) or via secondary messenger systems. Through activating second messengers, events on the cell surface may be amplified and cause intracellular changes.

The structure of the receptor is fundamental to its function and production of a specific response to ligand binding. The binding regions are unique to each receptor, but there are some common motifs between classes (Table 1.2).

Table 1.1 Mechanisms of drug action with clinical examples

Enzymes

Target	Inhibitor	Clinical effect and uses
Acetylcholinesterase	Neostigmine Pyridostigmine Organophosphates *Edrophonium*	Increase acetylcholine concentration at neuromuscular junction; reverse non-depolarising neuromuscular blockade. *Edrophonium,* rapidly reversible inhibitor of acetylcholinesterase, increases acetylcholine concentrations used to aid diagnosis of myasthenia gravis (improves symptoms) and cholinergic crisis (worsens symptoms). *Pyridostigmine* and *neostigmine* cause formation of a carbamylated enzyme complex with slow rate of acetylcholine hydrolysis and a long duration of action. *Organophosphates* cause irreversible inhibition of the enzyme, causing a cholinergic crisis.
Cyclo-oxygenase (COX)	Non-specific Aspirin Ibuprofen Diclofenac COX 2-specific Meloxicam Celecoxib	Anti-inflammatory; reduce production of prostacyclin, and leukotrienes. Salicylates (e.g. *aspirin*), propionic acids (e.g. *ibuprofen*), acetic acid derivatives (e.g. *diclofenac*) inhibit both COX-1 (constitutive) and COX-2 (inducible), reducing inflammation, but subject to renal injury and gastric erosions because of reduced constitutive production of protective prostaglandins. Oxicams (e.g. *meloxicam*) and pyrazoles (e.g. *celecoxib*) are COX-2 preferential, reducing the proinflammatory effects but without causing renal and gastric damage (although not in use because of increased cardiovascular risk).
Carbonic anhydrase	Acetazolamide	Reduced formation of carbonic acid; therefore causes urinary alkalinisation. Used as a diuretic, to correct alkalosis and in treatment of glaucoma.

Voltage-gated ion channel

Target	Activator	Inhibitor	Clinical effect and uses
Voltage-gated calcium channel		Verapamil Amlodipine Dipyridamole	Reduce nodal conduction and smooth muscle contraction; reduce chronotropy and vasodilation. Used to treat angina and tachyarrhythmias by blocking L-type calcium channels. Phenylalkylamines (e.g. *verapamil*) have preferential nodal action and are used to reduce heart rate. Dihydropyridines (e.g. *amlodipine*) and benzothiazepines (e.g. *diltiazem*) bind to calcium channels on smooth muscle, reducing vasoconstriction, lowering blood pressure.
Voltage-gated sodium channel		Lignocaine Bupivacaine Cocaine	Inhibit sodium channels, reducing depolarisation of nerves (and myocardium); used for local anaesthetic nerve blocks, topically for chronic pain. Occasionally used for antiarrhythmic effect. May be classified as amide (e.g. *lignocaine*) or ester (e.g. *cocaine*).
Voltage-gated potassium channel	Nicorandil		Potentiate opening of K^+ channels, hyperpolarising myocardial tissue and reducing myocardial work; also increases cGMP in smooth muscle, promoting relaxation.

Continued

Table 1.1 Mechanisms of drug action with clinical examples—cont'd

Ligand-gated ion channel			
Target	**Agonist**	**Antagonist**	**Clinical effect and uses**
$GABA_A$ receptor	Benzodiazepines		The $GABA_A$ receptor is a chloride channel found in diffuse areas of the brain. Benzodiazepines (e.g. *midazolam*) bind to an allosteric site, potentiating the response to native GABA, an inhibitory neurotransmitter, causing anxiolysis, hypnosis and amnesia.
Nicotinic AChR	suxamethonium	Rocuronium Atracurium	Nicotinic acetylcholine receptors are found at nerve synapses and on neuromuscular junctions. Depolarising neuromuscular blocking agents (NMBs) (e.g. *suxamethonium*) bind to and activate the channel, producing neuromuscular stimulation, rendering the muscle relaxed and refractory after initial stimulation. Non-depolarising NMBs may be aminosteroid (e.g. *rocuronium*) or benzylisoquinolone (e.g. *atracurium*). Both are nicotinic receptor antagonists preventing acetylcholine from binding and opening the channel.
Serotonin ($5\text{-}HT_3$)		Ondansetron	Found throughout the central nervous system, ligand-gated ion channel permeable to Na^+, K^+ and Ca^{2+}. Antagonism causes antiemesis.
Nuclear receptors			
Target	**Agonist**	**Antagonist**	**Clinical effect and uses**
Steroid receptors	Hydrocortisone Prednisolone		Reduce transcription of proinflammatory cytokines. All contain steroid nuclei, which are lipophilic, permitting intracellular passage and interaction with nuclear receptors and reduction of downstream transcription and protein synthesis.
G protein–coupled receptors			
Target	**Activator**	**Antagonist**	**Clinical effect and uses**
Opioid receptors ($G_{i/o}$)	Morphine	Naloxone	Opioid receptors cause reduction in cAMP, opening of potassium channels and reduction of intracellular calcium. This causes neuronal hyperpolarisation, analgesia, drowsiness, respiratory depression and constipation, the effects of opioid agonists such as *morphine*. *Naloxone* is an opioid antagonist, binding to the receptor but having no effect.
α_1-Adrenoceptors (G_q)	Phenylephrine	Doxazosin	Located on blood vessels and smooth muscle, cause vasoconstriction. *Phenylephrine* is a synthetic amine, a pure α_1 agonist, causing vasoconstriction. *Doxazosin* produces selective antagonism at α_1, reducing vasoconstriction, and is used in the treatment of hypertension.

Table 1.1 Mechanisms of drug action with clinical examples—cont'd

Target	Activator	Antagonist	Clinical effect and uses
α_2-Adrenoceptors (G_i)	Clonidine Dexmedetomidine	Yohimbine	Located presynaptically, reduces endogenous noradrenaline release and therefore sympathetic tone by reducing cAMP and opening potassium channels. *Clonidine* is used to treat hypertension, and the widespread distribution of α_1 adrenoceptors produces other effects such as analgesia, anxiolysis and sedation. *Yohimbine* reversibly antagonises the effects of α_2 agonists.
β_1-Adrenoceptors (G_s)	Isoprenaline	Atenolol	β_1 adrenoceptors are located in the myocardium and conducting system and predominately increase inotropy, chronotropy and dronotropy through increasing cAMP formation via G_s and adenylate cyclase. *Isoprenaline* is a synthetic catecholamine and a non-selective agonist at the β_1 adrenoceptor used in the treatment of bradycardias. *Atenolol* is a β_1 selective antagonist used in the treatment of hypertension and tachyarrhythmias.
β_2-Adrenoceptors (G_s)	Salbutamol		β_2 stimulation predominately causes bronchodilation. Salbutamol is a typical β_2 agonist, causing bronchodilation, and is used in the treatment of asthma. This may promote tachyarrhythmias and lactic acidosis through non-selective β_1 effects. There are no clinically useful β_2 antagonists.
Muscarinic receptors M_1 (postsynaptic) – G_q M_2 (cardiac) – G_i M_3 (smooth muscle) – G_q	Pilocarpine	Atropine Glycopyrronium bromide	Muscarinic receptors cause increases in salivation (M_1), bradycardias (M_2) and bronchoconstriction (M_3). *Pilocarpine* is used in the treatment of glaucoma to cause pupillary constriction and permit drainage of aqueous humour, reducing intraocular pressure. *Atropine* and *glycopyrronium bromide* are tertiary amines used in the treatment of bradycardias through antagonism at the muscarinic receptors.

Drugs acting via physicochemical mechanisms

Target	Mechanism	Drug	Clinical effect and uses
Acids	Neutralisation	Sodium citrate	Sodium citrate is used before general anaesthesia in obstetric practice to neutralise stomach acid.
Rocuronium	Chelation	Sugammadex	*Sugammadex*, a cyclodextrin, acts to engulf and chelate rocuronium, reversing its effect at the acetylcholine receptor
Multiple	Adsorption	Activated charcoal	Activated charcoal adsorbs various chemicals on to its surface preventing toxicity from their systemic absorption.

AChR, Acetylcholine receptor; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate.

Table 1.2 Structural features found in major receptor classes

Type	Structural features	Examples of drugs
Nuclear receptors	Zinc fingers	Steroids
Tyrosine kinase receptors	Dimers	Insulin
Ligand-gated ion channels	Multiple subunits, have a pore and ligand binding sites	Local anaesthetics
G protein–coupled receptors	7-transmembrane domains	Adrenaline

G protein–coupled receptors

The largest superfamily of receptors contains 7-transmembrane domains and couple to G-proteins. G protein–coupled receptors act as adapters between extracellular signalling and intracellular downstream second messenger systems, the endpoint of receptor activation (Fig. 1.4). Upon activation, the receptor undergoes a conformational change, causing the α subunit of the G protein to exchange bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP) (see Fig. 1.4A), which then causes it to dissociate from the G protein–coupled receptor and move to an effector molecule (see Fig. 1.4B). Whilst influencing the effector the bound GTP is hydrolysed to GDP by the GTPase of the α subunit (see Fig. 1.4C), which then returns to the intracellular

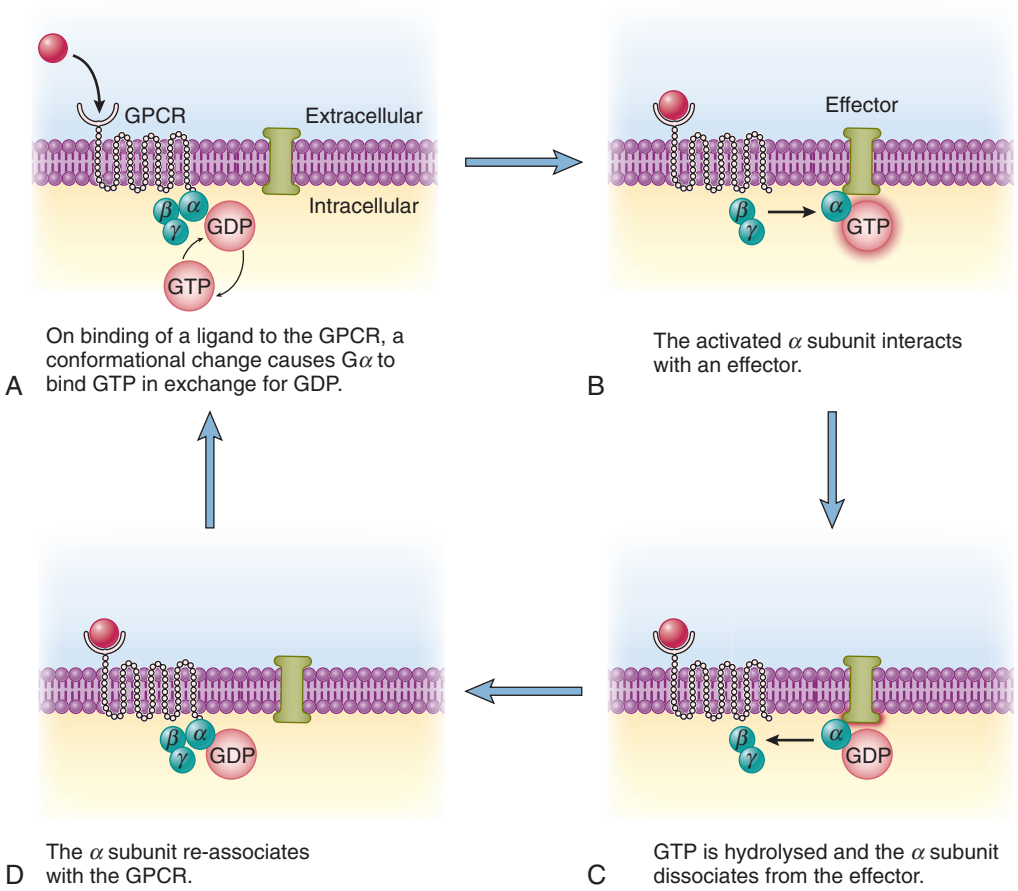

Fig. 1.4 Mode of action of G protein–coupled receptors. From the basal state (A), the binding of an agonist causes conformational change, and the G protein dissociates after exchanging guanosine triphosphate (GTP) for bound guanosine diphosphate (GDP). The α subunit interacts with an effector molecule (B), subsequently hydrolyses the bound GTP (C), and returns to the basal state (D).

Table 1.3 G-proteins and second messenger systems

G protein	Second messenger	Effect	Receptor and example of agonist drug
G_s	Adenylate cyclase	↑ cAMP	*Isoprenaline* (β-adrenoceptor)
G_i	Adenylate cyclase	↓cAMP	α_2 adrenoceptor *clonidine*
G_q	Phospholipase C	↑Ca^{2+}	α_1 adrenoceptor *phenylephrine*

cAMP, Cyclic adenosine monophosphate.

terminus of the receptor and reassociates with the βγ subunits (see Fig. 1.4D).

There are three major types of G protein (Table 1.3) capable of interacting with the second messengers adenylate cyclase ($G_{i/o}$ and G_s) and phospholipase C (G_q). A single receptor may activate many G proteins, and this amplifies the initial signal. Drugs can target different parts of this receptor cascade by interacting with the receptor (e.g. opioids), the G protein (e.g. botulinum toxin) or further downstream (e.g. Ca^{2+}).

Second messenger systems

Second messenger systems are the endpoint of a number of different inputs. They are a further level of amplification, enabling a small extracellular signal to effect a large and significant change to the intracellular environment.

Second messengers can enable other functions, such as protein phosphorylation. The result of protein phosphorylation can influenceion transport (e.g. acetylcholine, glutamate, γ-aminobutyric acid (GABA) receptors), and receptor activation state.

What influences the response of a receptor?

Ligands bind to receptors and are classified according to their effect, either to increase (agonist) or to have no effect (antagonist) on receptor response. Ligand-receptor kinetics, biological reactions and enzyme kinetics are all subject to the law of mass action, which states that the rate of reaction is proportional to the concentration of biologically active species present at a given time.

The classic rectangular hyperbolic dose–response relationship of an agonist is shown in Fig. 1.5A. As the number of agonist molecules increases, the receptor response increases until all binding sites are fully occupied and response is maximal (see Fig. 1.5A). This rectangular hyperbolic shaped curve is conventionally transformed to a semilogarithmic scale to produce a sigmoid-shaped curve that is approximately linear between 20% and 80% of maximum effect, allowing comparison of the effects of different agonists (see Fig. 1.5B). Agonists are described by the size of the effect they can produce (efficacy) and the dose required to elicit a given effect (potency).

The pEC_{50} is a log-transformed measure of the ligand concentration required to elicit a half-maximal response for the drug, a measure of potency. A rightward shift on the logarithmic scale indicates that the drug has lower potency; therefore an increased dose is required to achieve the same effect. Efficacy is the size of the response produced by ligand-receptor interaction. E_{MAX} is the maximal response. Therapeutic ligand-receptor interactions may produce unwanted adverse effects (such as the respiratory depression caused by agonism at the μ opioid receptor).

Full agonists can elicit a maximal effect, whereas partial agonists can never achieve maximum effect irrespective of dose and so have lower efficacy. Fig. 1.5B shows the effects of agonists A, B and C. B is less potent than A, but both are full agonists. B and C have the same potency, but C is a partial agonist as it is not able to elicit a full response, irrespective of concentration.

Antagonists bind to the receptor but produce no intrinsic effect. Competitive antagonists bind to the receptor, and displace endogenous ligands or other drugs therefore reducing receptor response. Non-competitive antagonists do not compete with endogenous ligands for the same binding site. They chemically or structurally modify the receptor, reducing the response induced by ligands occupying the binding site. Unlike competitive antagonists they cannot be overcome by increasing agonist concentration.

In the presence of a competitive antagonist, the log[dose]–response curve of an agonist is shifted to the right but the maximum effect remains unaltered (curves A and B in Fig. 1.5C). The effects of these antagonists can be overcome with an increasing agonist concentration. Examples of this

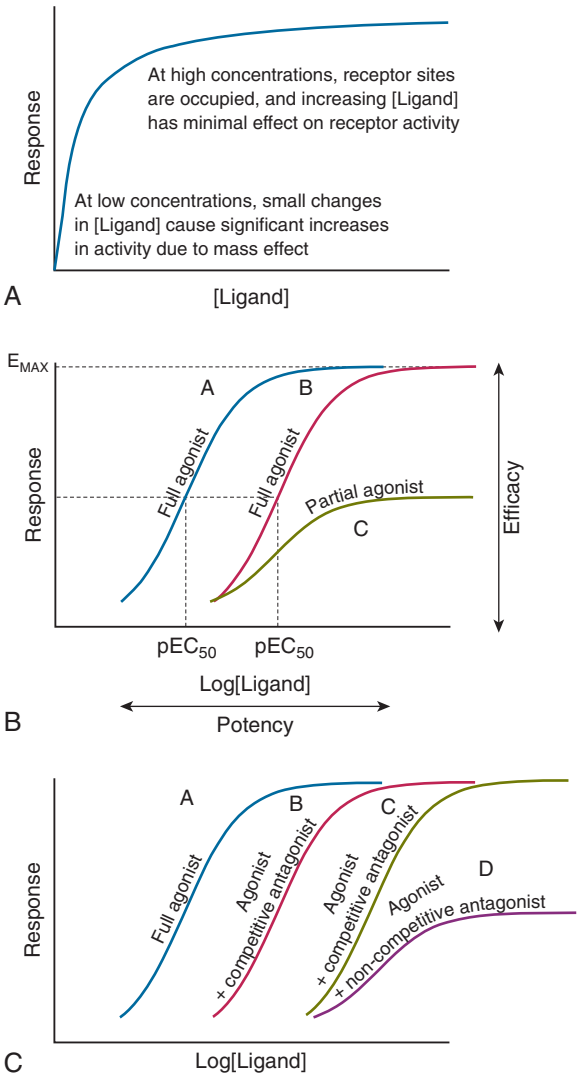

Fig. 1.5 Receptor response increases with ligand concentration for an agonist (A); the potency of different agonists may be compared by examining the pEC_{50} values after semilogarithmic transformation (B). The combination of agonists and antagonists causes a rightward shift of the curve (C, *curves A, B* and *C*). Irreversible non-competitive antagonists reduce the maximal response by reducing the available receptor pool (C, *curve D*).

effect include the displacement of morphine by naloxone and endogenous catecholamines by β-blockers.

A non-competitive (irreversible) antagonist also shifts the dose–response curve to the right but, with increasing concentrations, reduces the maximum effect (curve D in Fig. 1.5C) as the receptor pool is effectively limited. Examples of irreversible antagonism include the platelet inhibitors clopidogrel and aspirin. Organophosphates cause irreversible modification of acetylcholinesterase, causing increased cholinergic effects.

Drug actions on enzymes

An enzyme is a protein to which other molecules (substrate) may bind and undergo chemical modification in some way, such as breakdown or synthesis of other products. Drugs may act by binding reversibly or irreversibly to the active site of the enzyme and acting as substrates or to block binding of endogenous substrate. Some drugs bind to an alternative (allosteric) site to modify the activity of the enzyme.

Enzyme kinetics

The relationship between an enzyme, substrate and rate of reaction is described in Fig. 1.6A.

When an enzyme joins with appropriate substrate at the active site, the complex undergoes chemical modification to yield products. This equation (Eq. 1.3) is governed by the law of mass action, and therefore, where substrate concentrations are high, the equilibrium shifts to the right, favouring the generation of products.

$$Enzyme + Substrate \rightleftharpoons Complex \rightleftharpoons Enzyme + Products \quad \text{(Eq. 1.3)}$$

Where the substrate is at low concentration, its availability is rate limiting, whereas where substrate exceeds the enzyme's capacity, then enzymatic activity is the limiting factor.

Fig. 1.6A and B shows how, at low substrate concentrations, a small increase in substrate produces a significant increase in enzymatic activity, whereas at high substrate concentrations, the activity remains maximal and independent of substrate concentration. The effects of different enzymes are compared and modelled using the V_{MAX} (the maximal enzyme reaction rate) and k_M (substrate concentration at which half V_{MAX} is achieved).

Knowledge of enzyme kinetics is useful for predicting drug metabolism and pharmacokinetics. Drugs processed by first-order kinetics are metabolised by a large pool of enzymes and therefore overall enzyme activity is increased at high drug concentration; this increases the rate of metabolism and also reduces the chance of toxicity (Fig. 1.6C). However, where the enzymatic pool is small or the dose so high that the available enzymes become saturated, the rate of breakdown becomes fixed irrespective of drug concentration (Fig. 1.6D). This is known as zero order, or saturation kinetics, and is an important consideration in the metabolism of phenytoin, paracetamol and alcohol, sometimes requiring the monitoring of plasma drug concentrations.

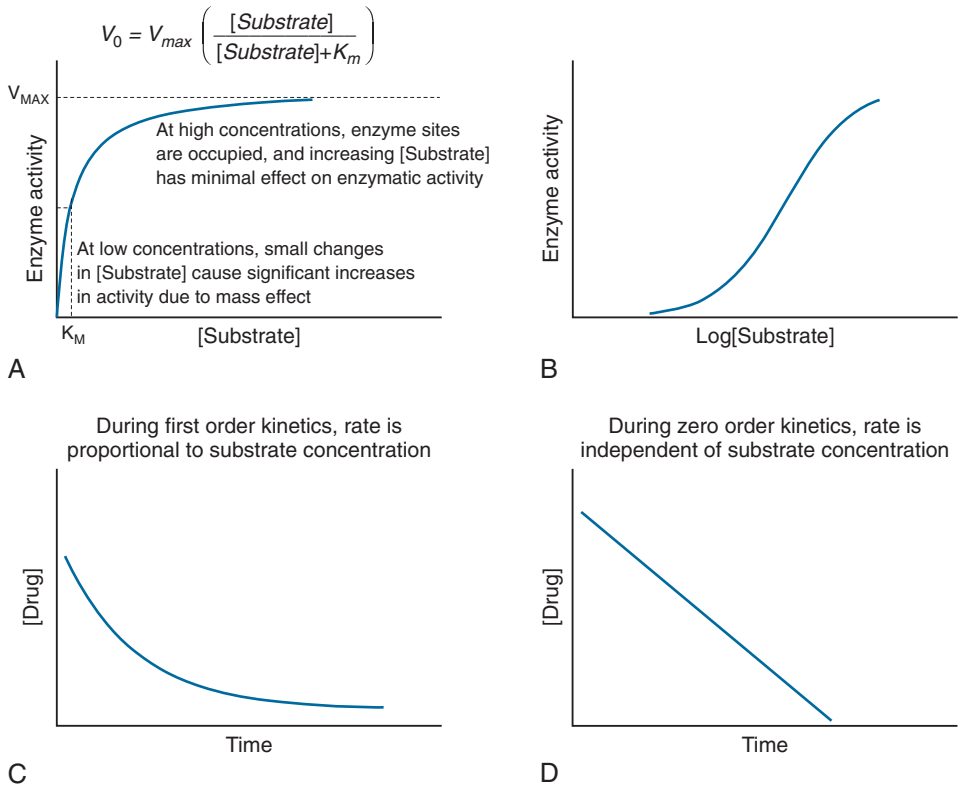

Fig. 1.6 Increasing concentrations of substrate cause increased enzyme activity (A and B) in a saturable manner. Initially, response is first order, proportional to the substrate concentration (C), but becomes zero order, independent of substrate concentration, when the number of substrate molecules exceeds the available binding sites (D).

Drugs may modulate enzymes by increasing or decreasing intrinsic activity or by competing with endogenous substrate molecules at the active site. As with receptor kinetics, reversible inhibition is caused by competition for the active site and may be overcome by an increase in the endogenous substrate. Examples include the reversible antagonism of acetylcholinesterase (by neostigmine), phosphodiesterase (by aminophylline), and angiotensin converting enzyme (by lisinopril). Irreversible enzyme inhibition occurs when a stable chemical bond is formed between drug and enzyme, resulting in prolonged or permanent inactivation. Examples include the irreversible inhibition of gastric hydrogen-potassium-ATPase (by omprazole), cyclo-oxygenase (by aspirin) and acetylcholinesterase (by organophosphates). *Allosteric modulation* refers to binding to a site other than the active site to influence enzyme activity – for example, the antiretroviral reverse transcriptase inhibitor efavirenz.

Physicochemical properties

The physicochemical properties of drugs produce other effects outside receptor, enzyme or secondary messenger pathways. These non-specific mechanisms often rely on physical properties such as pH, charge or physical interactions with other molecules (via chelation or adsorption).

pH-based interactions include the neutralisation of acid with alkali. Sodium citrate, aluminium and magnesium hydroxide neutralise gastric acid via this mechanism.

Chelating agents combine chemically with compounds, reducing their toxicity and enhancing elimination of the inactive complex. Such drugs include sugammadex (chelates rocuronium), deferoxamine (chelates iron and aluminium), dicobalt edetate (cyanide toxicity), sodium calcium edetate (lead) and penicillamine (copper and lead).

Molecular adsorption describes the interaction and binding of a molecule to the surface of another, reducing the

free fraction available for absorption from the gastrointestinal tract. This mechanism may be useful in the treatment of drug toxicity to prevent an oral overdose from being absorbed (activated charcoal) or in the management of hyperkalaemia (calcium resonium reduces the GI absorption of potassium).

How does the body process drugs (pharmacokinetics)?

Absorption

Absorption describes the process by which a drug is taken up from the initial site of administration into the blood. The rate and amount of absorption affects the final plasma concentration and therefore drug concentration at the effect site. For drugs requiring multiple doses, these principles will also affect peak plasma concentration and time to maximal concentration.

Absorption is influenced by factors specific to both drug and patient, as discussed earlier. The pathway from site of administration to final effect site includes passage across membranes and blood transport (see Transport of drugs and Routes of administration). Drugs may have specific formulations which affect the rate of drug release or facilitate delivery to the target site. These are covered in more detail in Pharmacokinetic principles.

Distribution

Protein binding

Many drugs are bound to proteins in the plasma; this permits transport around the body but reduces the active unbound, ionised drug fraction. Changes in protein binding may therefore have significant effects on the active unbound concentration of a drug and thus its actions.

Albumin is the most important and abundant protein contributing to drug binding and is responsible mainly for the binding of acidic and neutral drugs. Globulins, especially α_1-acid glycoprotein, bind mainly basic drugs. If a drug is highly protein bound (>80%), any change in plasma protein concentration or displacement of the drug by another with similar binding properties may have clinically significant effects. For example, most NSAIDs displace warfarin, phenytoin and lithium from plasma binding sites, leading to potential toxicity.

Plasma albumin concentration is often decreased in the elderly, in neonates and in the presence of malnutrition, liver, renal or cardiac failure and malignancy. α_1-acid glycoprotein concentration is decreased during pregnancy and in the neonate but may be increased in the postoperative period, in infection, trauma, burns and malignancy.

Metabolism

Most drugs are lipid soluble, and the majority are metabolised in the liver. Metabolites are mostly pharmacologically inactive, ionised (water soluble) compounds which are then excreted in bile or by the kidneys. However, some metabolites may be active and cause prolonged clinical effect after the parent compound has been broken down or removed from the circulation. Some drugs are metabolised outside the liver (by kidneys, lungs, plasma and tissues).

Medications that are absorbed enterally undergo first-pass metabolism before passing from the portal circulation into the systemic circulation.

First-pass metabolism may increase or decrease drug effect to a variable extent. A substance is termed a *prodrug* if it is inactive in the form administered and its pharmacological effects depend on the formation of active metabolites. Codeine is a prodrug, undergoing metabolism via gluconuridation (50%–70%), *N*-demethylation (10%–15%) and *O*-demethylation (0%–15%). Morphine, resulting from *O*-demethylation of codeine by CYP2D6, is the most active metabolite and has greater activity at the opioid receptor. CYP2D6 exists as slow, rapid and ultra-rapid phenotypes, which affect the therapeutic response to codeine. Those with inactive CYP2D6 may derive no analgesia from codeine, whereas ultra-rapid metabolisers may have significant drowsiness, respiratory depression and features of opiate toxicity.

Drugs undergo two types of reactions during metabolism: phase I and phase II. Phase I reactions include reduction, oxidation and hydrolysis. Drug oxidation occurs in the smooth endoplasmic reticulum, primarily by the cytochrome P450 enzyme system. This system and other enzymes also perform reduction reactions. Hydrolysis is a common phase I reaction in the metabolism of drugs with ester or amide groups (e.g. meperidine). Amide drugs often undergo hydrolysis and oxidative *N*-dealkylation (e.g. lidocaine, bupivacaine).

Phase II reactions involve conjugation of a metabolite or the drug itself with an endogenous substrate. Conjugation with glucuronic acid is a major metabolic pathway, but others include acetylation, methylation and conjugation with sulphate or glycine.

Extra-hepatic or extra-renal metabolism is independent of liver or renal function. Typically this leads to a rapid offset of drug action because of the abundance of enzyme sites for metabolism. Drugs metabolised via these routes can be useful in those with hepatic or renal failure. For example, suxamethonium and mivacurium are metabolised by plasma cholinesterase, esmolol by erythrocyte esterases, remifentanil by tissue esterases and, in part, dopamine by the kidney and prilocaine by the lungs. Occasionally drugs will undergo spontaneous degradation to generate active or inactive metabolites. These processes are also independent

of hepatic or renal pathways – such as the spontaneous breakdown of atracurium by Hofmann degradation.

Elimination

Ionised compounds with a low molecular weight (MW) are excreted mainly by the kidneys. Most drugs and metabolites diffuse passively into the proximal renal tubules by the process of glomerular filtration, but some are secreted actively (e.g. penicillins, aspirin, many diuretics, morphine, lidocaine and glucuronides). Ionisation is a significant barrier to reabsorption at the distal tubule. Consequently, basic drugs or metabolites are excreted more efficiently in acidic urine and acidic compounds in alkaline urine. Urinary alkalinisation is sometimes used in the treatment of aspirin and tricyclic antidepressant overdose.

Some drugs and metabolites, particularly larger molecules (MW >400 D), are excreted in the bile (e.g. glycopyrronium bromide, vecuronium, pancuronium and the metabolites of morphine and buprenorphine). Ventilation is responsible for excretion of volatile anaesthetic agents.

Pharmacokinetic principles

Pharmacokinetics describes the processing of a drug by the body. This allows modelling of the likely behaviour and actions of a drug in the body and enables predictions of plasma concentration and clinical effect at a given time. Important variables are volume of distribution (V_D), clearance (Cl) and half-life ($t_{1/2}$). Whilst pharmacokinetic predictions and models have generic value, the effects in an individual depend on existing physiology, age, disease, drug interactions and other factors.

Compartment models

For simplicity, drug pharmacokinetics are usually described using one-, two- or three-compartment models (Fig. 1.7). Drugs are added to and eliminated from a central plasma compartment and equilibrate with peripheral tissues and the effect site (see Fig. 1.7 A, B, and C respectively). The rate of equilibration depends on the drug (p*Ka*, degree of ionisation, lipid solubility, formulation), route of administration, regional blood flow and compartment sizes.

When a drug is administered and reaches the central compartment, the plasma concentration initially increases rapidly and then falls as the drug passes into the other compartments and later is eliminated completely. The changes in measured plasma drug concentration during the time for absorption, redistribution and elimination are represented as an exponential decay (Fig. 1.8). The simplest model, a single compartment, represents plasma concentration decline only as a result of metabolism or clearance, whereas two- and three-compartment models include concentration changes caused by redistribution into other tissues, a more physiological approximation.

The rate at which drug distribution and subsequent elimination occurs is described in terms of equilibria between the various compartments (see Fig. 1.7). These are additive and result in concentration–time curves with two or three phases of decay attributable to redistribution (rapid and slow in the three-compartment model) and elimination.

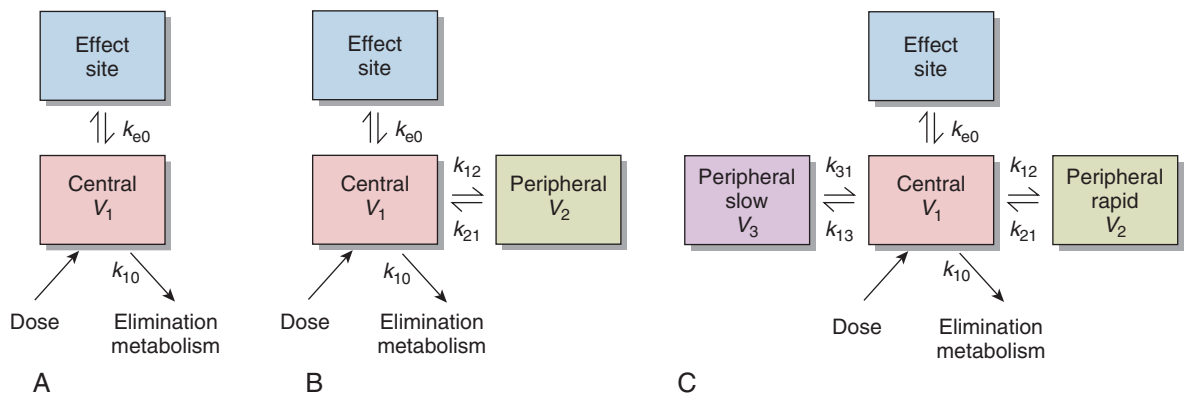

Fig. 1.7 Pharmacological compartments are described as one-, two-, or three-compartment models (A, B or C). Each compartment consists of a central region from which drug is added or removed, the effect site, and other areas within which drugs may be sequestered. The different models have peripheral compartments of varying vascularity to simulate equilibria and model pharmacokinetic drug characteristics.

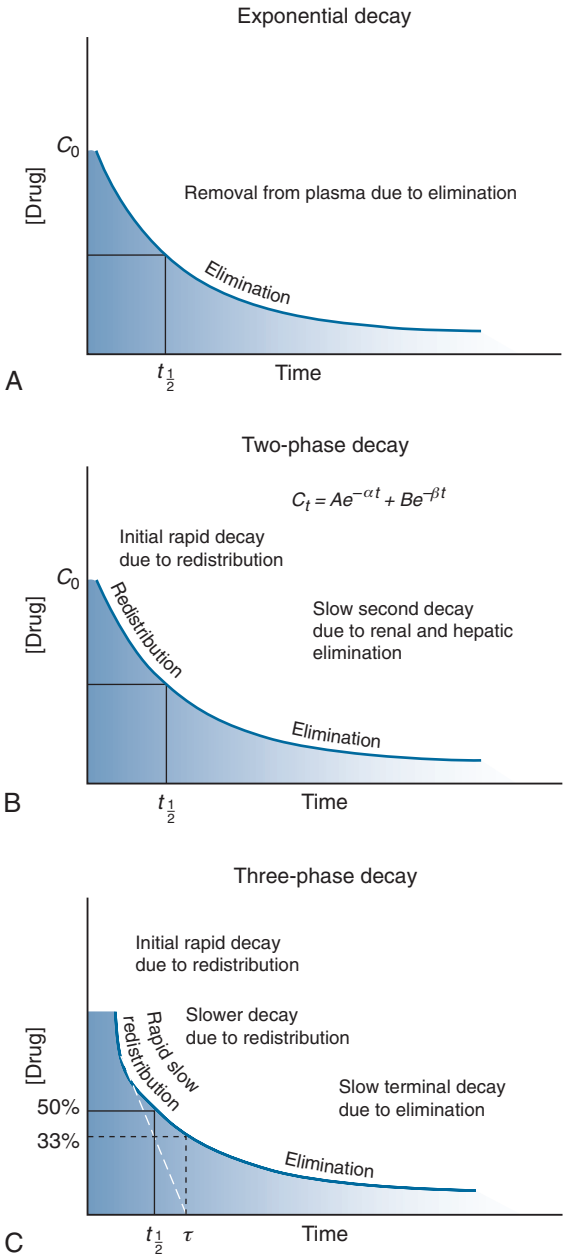

Fig. 1.8 Exponential decay is when the fall in concentration depends on the amount of substance present at a given time. Therefore constant proportion of substance disappears per unit time. The phases relate to the number of compartments for redistribution and the terminal elimination.

The equilibria, k_{12} and k_{13}, both influence drug concentration at the final effect site (k_{e0}) and for elimination (k_{10}). The resultant concentration–time curve is a one-, two- or three-phase exponential decay (see Fig. 1.8).

In the two-compartment model, one compartment represents the plasma and the other represents the remainder of the body. In this model, after intravenous injection of a drug, the plasma concentration (C_P) decreases because of removal by elimination and redistribution into peripheral tissues. Fig. 1.8C shows the relationship between the *half-life* ($t_{1/2}$, time for the starting concentration to decay by 50%) and *time constant* (τ, the time to completion if the initial rate of change continued, or the time to decay to 33% of the initial concentration).

If the natural logs of the concentrations are plotted against time (semi-logarithmic plot), a straight line is produced in one, two or three phases depending on the compartment model used (Fig. 1.9A and B and C).

Consider a single-compartment model (see Fig. 1.8A and Fig. 1.9A). The concentration–time plot indicates $t_{1/2}$. After semilogarithmic transformation (see Fig. 1.9A), the gradient of this line (k) and the initial concentration (C_0) can be extrapolated. The gradient is the elimination rate constant k, which is related to $t_{1/2}$ in the following equation (Eq. 1.4):

$$k = \frac{ln2}{t_{1/2}} \qquad \text{(Eq. 1.4)}$$

Using the concentration–time plots and their semilogarithmic transformations, the concentration at any time can be described in terms of an exponential decay (Eq. 1.5)

$$C_P = C_0 e^{-kt} \qquad \text{(Eq. 1.5)}$$

where t is the time after administration, k is the elimination rate constant, C_0 is the initial concentration and C_P is the plasma concentration at time t.

In the two- and three-compartment model, (Fig. 1.9B and C) the plasma concentration at a given time t represents the sum of the decay processes. The two lines α and β represent decline by redistribution and elimination, respectively, each of which have their own k values (α and β), starting concentrations (A and B) and half-lives ($t_{1/2\alpha}$, $t_{1/2\beta}$).

These biexponential decays are modelled using standard exponential equations (see Eq. 1.5), and therefore C_P at any time in a two-compartment model after bolus intravenous administration is the sum of the elimination and redistribution phases (Eq. 1.6).

$$C_P = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1.6)}$$

where α and β are the redistribution and elimination rate constants, respectively, and A and B are the extrapolated

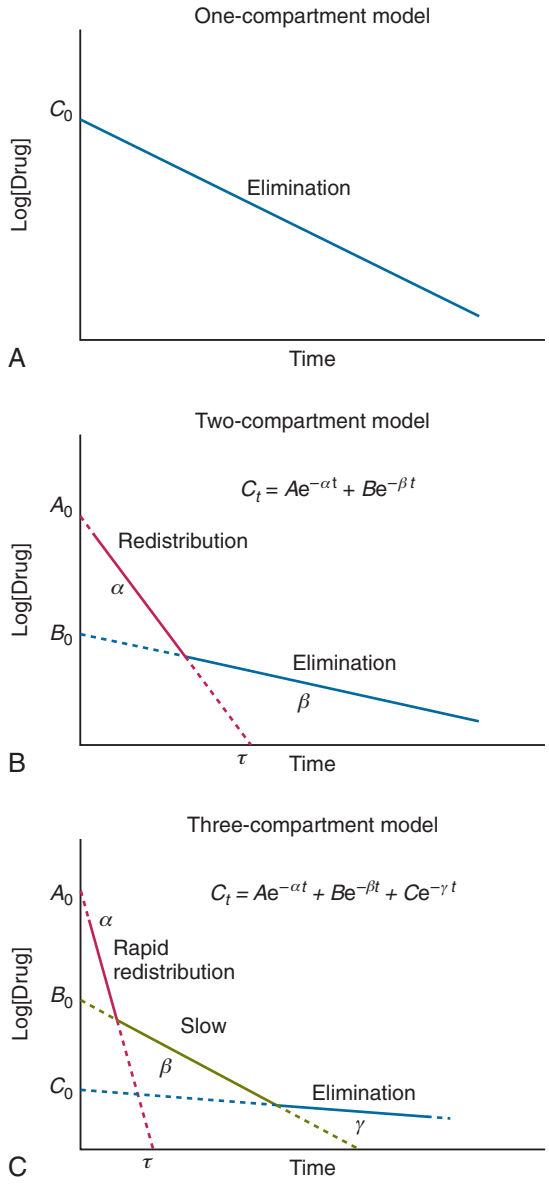

Fig. 1.9 Semilogarithmic transformation of concentration–time curves demonstrates a single-phase, biphasic and triphasic exponential decay. This transformation generates linear relationships for each of the phases of redistribution and elimination, allowing the calculation of initial concentration C_0, concentration at a given time, and therefore bolus or infusion requirements to achieve steady state.

starting points (see Fig. 1.9). In the three-compartment model, drug redistribution is initially rapid to well-perfused tissues and then slow into poorly perfused areas before terminal elimination, a triexponential model.

After drug administration, the clinical effect depends on the drug reaching the site of action from the central compartment. Half of this equilibration occurs in $t_{1/2}\ k_{e0}$. Therefore the $t_{1/2}\ k_{e0}$ reflects time to peak concentration at the effect site and thus time to peak clinical effect. Equilibration at the effect site during an i.v. drug infusion occurs in four to five half-lives ($t_{1/2}\ k_{e0}$), which is the time to change in effect after a change of infusion rate.

Volume of distribution

Volume of distribution is the theoretical volume into which a drug distributes immediately to give the plasma concentration observed at that time. As the concentration cannot be measured instantaneously, semilogarithmic plots (see Fig. 1.9) allow the initial concentration to be derived by extrapolation. Where the dose given and initial plasma concentration are known (C_0), the volume of distribution (V_D) may be calculated by rearranging Eq. 1.7 to form Eq. 1.8.

$$C_0 = \frac{dose}{V} \qquad \text{(Eq. 1.7)}$$

where C_0 is the initial concentration. Therefore:

$$V_D = \frac{dose}{C_0} \qquad \text{(Eq. 1.8)}$$

A more accurate measurement of V_D is possible during constant-rate infusion when the distribution of the drug in the tissues has time to equilibrate; this is termed volume of distribution at steady state (V_{Dss}).

Large, water-soluble, polar drugs that remain in the plasma and do not pass easily to other tissues have a small V_D and therefore a large C_0. Other factors such as plasma protein binding also reduce diffusion out of the plasma. Drugs with a large V_D are often lipid soluble and therefore accumulate in tissues outside the plasma (e.g. intravenous anaesthetic agents).

Some drugs accumulate outside the plasma, making values for V_D greater than total body water volume. Large V_D values are often observed for drugs highly bound to proteins outside plasma (e.g. local anaesthetics, digoxin).

Several factors may affect V_D and therefore C_0 after bolus injection of a drug. Patients who are dehydrated or have lost blood have a significantly greater plasma C_0 after a normal dose of intravenous anaesthetic agent, increasing the likelihood of concentration-dependent adverse effects. In the case of intravenous anaesthetics, this often manifests as haemodynamic instability caused by cardiac depression

and reduced vascular tone. Neonates have a proportionally greater volume of extracellular fluid compared with adults, and water-soluble drugs (e.g. neuromuscular blockers) tend to have a proportionally greater V_D. Factors affecting plasma protein binding (see earlier) may also affect V_D.

Finally, V_D can give some indication of the half-life. A large V_D is often associated with a relatively slow decline in plasma concentration; this relationship is expressed in a useful pharmacokinetic equation (Eq. 1.9–1.10).

Elimination

Elimination describes the removal of active drug from the body, which may include renal excretion, metabolism to other forms or elimination via bile, sweat or exhalation.

Drug half-life can be derived from the plasma concentration–time graph (see Fig. 1.8) but is also related to clearance and to metabolism (Eq. 1.9).

$$t_{1/2} \propto \frac{V_D}{Cl} \qquad \text{(Eq. 1. 9)}$$

or

$$t_{1/2} = constant \times \frac{V_D}{Cl}$$

The constant in this equation (elimination rate constant) is the natural logarithm of 2 (ln 2) – that is, 0.693. Therefore:

$$t_{1/2} = 0.693 \times \frac{V_D}{Cl} \qquad \text{(Eq. 1.10)}$$

For simple receptor–ligand equilibria, half-life reflects duration of drug action, although where binding or action is irreversible or active metabolites are produced, the clinical effect will be prolonged relative to the plasma $t_{1/2}$.

Clearance

Clearance is defined as the volume of blood or plasma from which the drug is removed completely per unit time. Drugs may be eliminated from the blood by the liver, kidney or occasionally other routes (see earlier). The relative proportion of hepatic and renal clearance of a drug is important. Most drugs used in anaesthetic practice are cleared predominantly by the liver, but some rely on renal or non–organ-dependent clearance. Excessive accumulation of a renally cleared drug may occur in patients in renal failure. For example, morphine is metabolised primarily in the liver, and this is not affected significantly in renal impairment. However, the active metabolite morphine-6-glucuronide is excreted predominantly by the kidney.

As with volume of distribution, clearance may predict the likely properties of a drug. For example, if clearance is greater than hepatic blood flow, factors other than hepatic metabolism must account for its total clearance. Apparent clearance greater than cardiac output may indicate metabolism in the plasma (e.g. suxamethonium) or other tissues (e.g. remifentanil). Clearance is an important (but not the only) factor affecting $t_{1/2}$ and steady-state plasma concentrations achieved during constant-rate infusions (see later).

Clearance may be derived also by calculation of the area under the concentration–time curve (see Fig. 1.8) extrapolated to infinity (AUC_∞) and substituted into Eq. 1.11.

$$Cl = \frac{dose}{AUC_\infty} \qquad \text{(Eq. 1.11)}$$

Metabolism

Enzyme induction and inhibition

Some drugs may enhance the activity of enzymes responsible for hepatic metabolism, particularly the family of cytochrome P450 enzymes and glucuronyl transferase. Drugs enhancing enzyme activity include phenytoin, carbamazepine, barbiturates, ethanol, steroids and some inhalational anaesthetic agents (halothane and enflurane). Cigarette smoking also induces cytochrome P450 enzymes.

Drugs with a non-enzymatic primary mechanism may also have secondary interactions with enzyme systems. For example, etomidate inhibits the synthesis of cortisol and aldosterone – an effect which may explain the increased mortality observed when it was used as a sedative agent in the critically ill. Cimetidine is a potent enzyme inhibitor and may prolong the elimination of drugs such as diazepam, propranolol, oral anticoagulants, phenytoin and lidocaine. Troublesome interactions with enzyme systems can be unpredictable and are not always clear until the early stages of testing in phase 2 or 3 studies.

Routes of administration

Oral

The oral route of drug administration is often the most convenient when it is available. However starvation for anaesthesia or the pathophysiological effects of disease sometimes preclude enteral administration. Absorption from the gut is affected by drug- and patient-based physiological and pathological processes.

Drug and physiological factors relating to the passage of drugs across membranes have been considered previously. Drug formulation is an important consideration; tablets or capsules are more poorly absorbed than liquids, and some drugs may be given as slow release or enteric-coated modified release preparations. The combination of naloxone and oxycodone found in the drug targinact is an example

of the local delivery of (non-absorbable) naloxone to the gastrointestinal tract to counteract the constipation caused by the (absorbed) oxycodone acting on local μ opioid receptors in the bowel.

The rate of absorption, and therefore effect of the drug, may be influenced significantly by its molecular size, lipid solubility and formulation. Most preparations dissolve in gastric acid, and the drug is absorbed in the small bowel after passing through the stomach; therefore formulations suitable for oral administration must not be subject to breakdown by stomach acid or peptidases.

Enterally administered drugs are subject to first-pass metabolism, and this can affect the dose required to achieve a given plasma concentration.

Gastric emptying

Most drugs are absorbed only when they have left the stomach. The effects of surgery can delay gastric emptying and promote ileus. This can affect absorption and can lead to drug accumulation in the stomach, risking unpredictable effects on plasma concentrations and clinical action.

Any factor increasing upper intestinal motility (such as drugs, surgery or the effects of autonomic dysfunction) reduces the time available for absorption and may decrease the total amount of drug absorbed.

Bioavailability

Oral bioavailability is the percentage of an enterally administered drug dose which is absorbed into the systemic circulation. This is derived from a graph of plasma concentration against time for both oral and intravenous administration of the same dose of drug in a given individual on separate occasions (Fig. 1.10). Bioavailability is calculated as the ratio of the areas under the concentration–time curves for oral, and i.v. administration. A high bioavailability indicates that a high proportion of the orally administrated dose reaches the effect site, and indicates suitability oral administration (e.g. codeine >90%), whereas the opposite is true for low bioavailability, requiring administration via a non-enteral route (e.g. glyceryl trinitrate <1%).

Lingual, buccal and nasal

The oral mucosa has a rich blood supply, and therefore lipid-soluble drugs are absorbable via this route. The avoidance of first-pass metabolism and rapid absorption make this an ideal route for some drugs, such as fentanyl, buprenorphine and glyceryl trinitrate.

The nasal mucosa has a rich blood supply, is readily accessible and avoids first-pass metabolism. The rapid absorption afforded by this route allows use where intravenous access is not practical, such as for paediatric sedation or analgesia

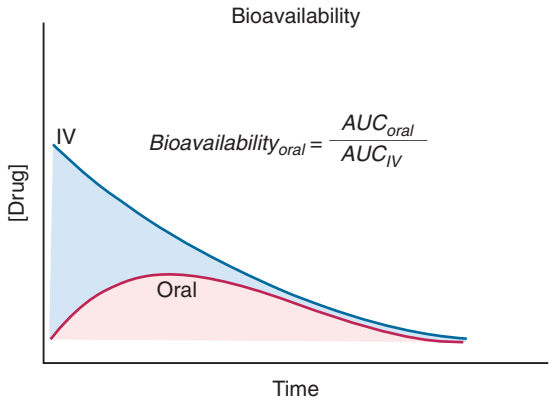

Fig. 1.10 Oral bioavailability is the ratio of the areas under the plasma concentration–time curves for enteral and parenteral routes of administration.

using midazolam or diamorphine. Topical drugs are used to facilitate nasal surgery, although the rich blood supply risks systemic toxicity and is often offset with the addition of a vasoconstrictor such as phenylephrine or adrenaline (e.g. coadministration of lignocaine and phenylephrine in nasal surgery for analgesia and to reduce bleeding).

Intramuscular and subcutaneous

Both intramuscular and subcutaneous routes avoid the need for intravenous access, the effects of first-pass metabolism and the rapid increases in plasma drug concentration seen with i.v. boluses. However, differences in regional blood flow to the skin and to muscles affects absorption unpredictably. Intramuscular administration can be particularly painful.

Variations in absorption may be clinically relevant. For example, peak plasma concentrations of morphine may occur at any time from 5 to 60 minutes after intramuscular administration, resulting in unreliable analgesia.

Intravenous

The intravenous characteristics of drugs vary depending on whether they are given as a bolus or as fixed, variable rate or target controlled infusions. Using the intravenous induction agent propofol as an example, the effects of these modes are described in Fig. 1.11 and in the following sections.

Bolus

The majority of drugs used in anaesthetic practice are given by intravenous bolus. This is a convenient and rapid method of drug delivery. However, it requires intravenous access. Plasma concentrations of propofol rise rapidly after intravenous bolus administration. This results in a fast onset of clinical effect because the propofol crosses the blood–brain

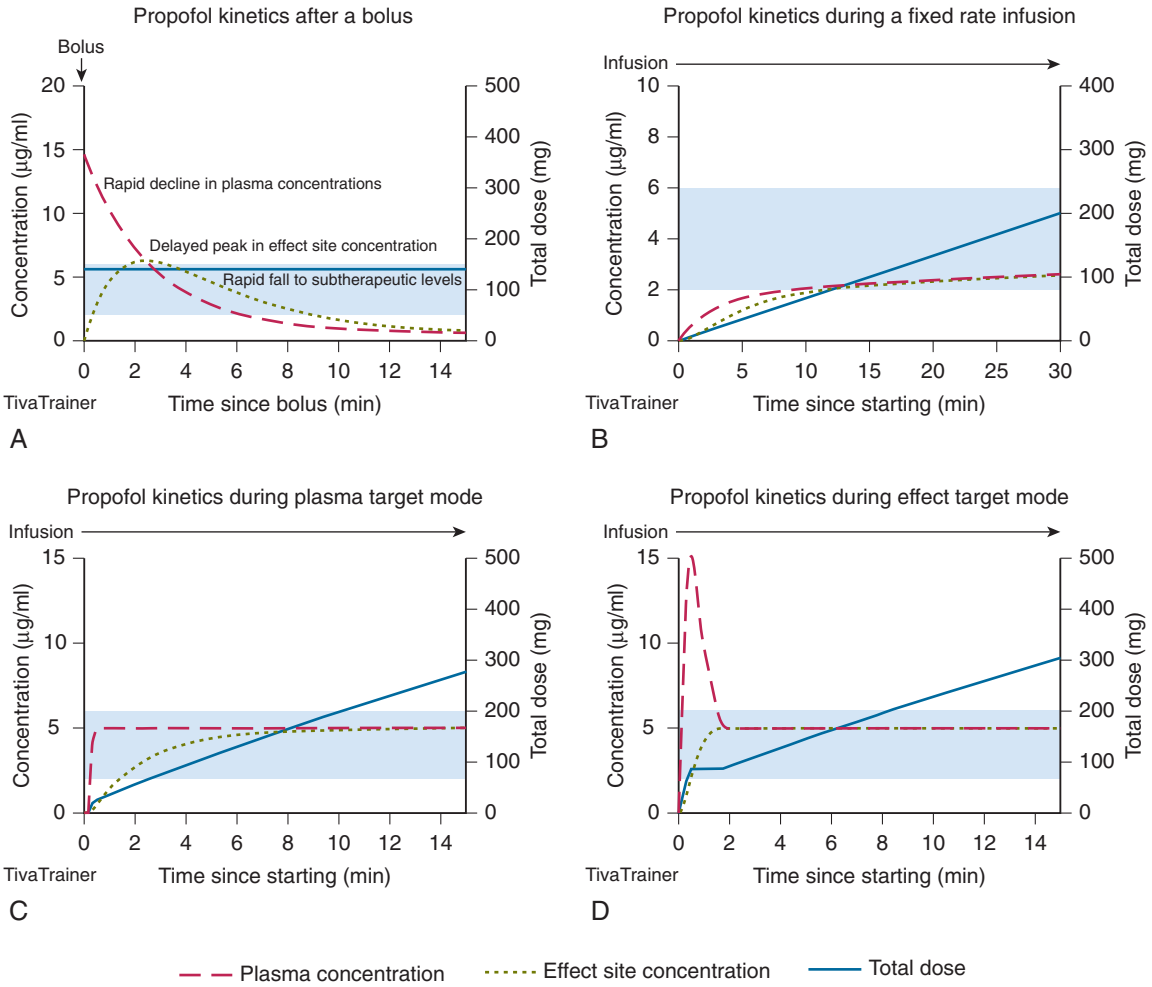

Fig. 1.11 Kinetics of propofol given as (A) bolus, (B) fixed rate infusion, (C) target controlled Schnider plasma concentration or (D) target controlled Schnider effect site. All data are for a 70-kg man, targeted at 5 mcg ml^{-1}. Therapeutic range shaded. (Data derived from Tivatrainer Simulation Software, Gutta BV, Aerdenhout, the Netherlands.)

barrier rapidly with its concentration gradient to reach its effect site. Plasma concentration falls quickly with offset of clinical effect as the drug redistributes (see Fig. 1.11A). As propofol is highly lipid soluble, offset is rapid and occurs because of redistribution from the effect site. Overshoot is a concern following bolus administration of drugs with a narrow therapeutic index. Therefore it is an important general rule that drugs administered intravenously should be given slowly and titrated to effect, except where there is a clinical need such as in rapid sequence induction.

Plasma concentration after an intravenous bolus dose is determined by the dose, speed of injection and cardiac output. Therefore an elderly, sick or hypovolaemic patient undergoing intravenous induction of anaesthesia is likely to suffer significant side effects if the drug is given at the same dose or rate as would be used in a normal, healthy young adult.

Infusions

Fixed-rate infusions

Drugs may be given by constant-rate infusion, a method often used for propofol, neuromuscular blocking agents, opioids and many other drugs. Plasma concentrations achieved during fixed rate infusions may be described by a wash-in exponential curve (see Fig. 1.11B).

When starting or adjusting an infusion rate, a steady state plasma concentration is achieved within four to five plasma half-lives for the individual drug. As $t_{1/2}$ is the main factor influencing time to achieve steady state, use of fixed rate infusion for drugs with a short half life can avoid significant accumulation and achieve steady state rapidly. During and after infusion, drugs equilibrate between central and peripheral compartments through redistribution. To maintain a steady state plasma concentration, therefore, the rate of drug infusion must be equal to the rate of removal through redistribution and elimination. However, the clinical effect is determined by $t_{1/2}$ k_{e0}, which relates to effect site concentration rather than plasma concentration.

The rate of a fixed infusion required to achieve a given steady state plasma concentration is dependent on drug clearance (Eq. 1.12).

$$Rate\ of\ Infusion = Cl \times C_{SS} \qquad \text{(Eq. 1.12)}$$

Eq. 1.12 shows the relationship between clearance and steady-state concentration for drugs delivered via infusions at a given rate, where C_{ss} is the steady state plasma concentration.

Many pathological conditions reduce drug clearance and may therefore result in unexpectedly high plasma concentrations during infusions. Half-life does not influence C_{ss}, only how quickly it is achieved.

Total intravenous anaesthesia and target controlled infusions

Total intravenous anaesthesia (TIVA) refers to the practice of administering anaesthesia via a continuous intravenous infusion, commonly either as fixed rate or via a computer-controlled pump. TIVA algorithms are designed to achieve and maintain a steady-state plasma or effect site concentration, by administering an initial bolus followed by an infusion (see Fig. 1.11B–D). Target controlled infusions deliver the drug according to pharmacokinetic models to give a predicted plasma or effect site concentration based on assumptions about compartment size, clearance and the effects of redistribution based on equations 1.13–1.16 below.

$$\frac{\text{Dose}}{\text{Volume}} = \text{Concentration} \qquad \text{(Eq. 1.13)}$$

$$\text{Dose} = \text{Volume} \times \text{Concentration} \qquad \text{(Eq. 1.14)}$$

$$\text{Loading dose} = V_{DSS} \times \text{Plasma concentration} \qquad \text{(Eq. 1.15)}$$

$$\text{Infusion rate} = \text{Cl} \times \text{Plasma concentration} \qquad \text{(Eq. 1.16)}$$

Pharmacokinetic models are drug specific and tailored to adults or children. Models in common use include include Marsh, Schnider and Paedfusor (propofol), and Minto (remifentanil). Models exist for adult and for paediatric practice to take into account the differences in compartment size and physiology. These allow targeting to effect site (C_e) or plasma (C_p) concentration.

The Schnider model is used for propofol infusions and uses a fixed central compartment volume of 4.7 l. Volumes of the other compartments, the rate constants and elimination rate constant are determined by age, weight and lean body mass as calculated by the pump's algorithm. When running in C_P mode (see Fig. 1.11C), a small initial bolus is given, followed by an infusion, whereas in C_e mode (see Fig. 1.11D), the bolus is larger to account for equilibration with the effect site. In both modes there is a lag between the increase in plasma concentration and effect site concentration because of the time taken for equilibration. The time to peak effect is related to the half-life.

Context-sensitive half-time

Following administration by an infusion, the drug will have redistributed into more peripheral compartments to a variable extent, depending on its V_D, clearance and the duration of the infusion. When the infusion is stopped, the drug redistributes along concentration gradients, back into the plasma and effect sites. Hence the offset of clinical effect can be unpredictable, as it depends on the dose, duration of infusion, intrinsic properties of the drug and factors such as metabolism and organ function. Predictably, a drug with high V_D and high intrinsic clearance should have a similar half-life to a drug with low V_D and clearance – however, this is not the case. Therefore the context-sensitive half-time (CSHT) gives a realistic model for drug behaviour after prolonged infusion.

Context-sensitive half-time is defined as the time taken for the plasma concentration to decrease by half after stopping an infusion designed to maintain a steady-state concentration; CSHT allows some prediction of how long drug effects persist after an infusion is stopped.

Comparing the opioids fentanyl, remifentanil, alfentanil and morphine (Fig. 1.12) illustrates some aspects of their clinical pharmacology in practice. The CSHTs for fentanyl and morphine increase steadily with infusion duration, whereas the increase for alfentanil is shallower and plateaus. Remifentanil has a fixed, flat CSHT irrespective of infusion duration.

Remifentanil is rapidly broken down by non-specific esterases, resulting in a short CSHT independent of infusion duration. Fentanyl is highly lipid soluble and has high intrinsic clearance. However, the very large V_D at steady state results in significant accumulation after infusion or repeated boluses. Therefore, prolonged infusion of fentanyl can result in delayed offset. The p*K*a and relative insolubility of alfentanil result in a smaller V_D and a lower CSHT, although there is some accumulation and delayed offset after an infusion because intrinsic clearance of the drug is low. Morphine accumulates, and offset is further delayed

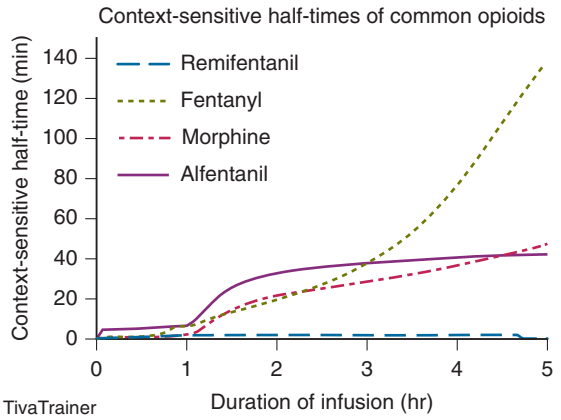

Fig. 1.12 Comparison of context-sensitive half-times for remifentanil, fentanyl, morphine and alfentanil. All data are for a 70-kg man. (Data derived from Tivatrainer Simulation Software, Gutta BV, Aerdenhout, the Netherlands.)

after a sustained infusion because of a large V_D, which is not overcome by a relatively high clearance.

Rectal

The rectal route negates first-pass metabolism and may be used where the enteral route is unavailable. It is used in children and adults (e.g. for delivery of paracetamol, diclofenac or ibuprofen) for postoperative analgesia. The proportion of drug absorbed via this route is highly variable.

Transdermal

Drugs with a high lipid solubility and potency may be given transdermally. Drug effects locally or systemically depend on the drug crossing the dermis in sufficient quantities. The drug is either embedded in a patch with a reservoir and membrane to control delivery or in a matrix that promotes slow continuous release.

The most commonly used transdermal medications in anaesthetic practice are the local anaesthetic creams (e.g. lidocaine/prilocaine (EMLA), tetracaine (Ametop)). Here the intent is to allow sufficient transdermal penetration to achieve local anaesthesia, but without causing excessive plasma concentrations. Local absorption is encouraged by use of high concentrations and occlusive dressings.

Glyceryl trinitrate is sometimes administered transdermally for the relief of local vascular insufficiency or for the systemic treatment of ischaemic heart disease. Glyceryl trinitrate is ideal for this indication as it is potent, highly lipid soluble and has a short half-life. Transdermal administration avoids first-pass metabolism and may be used where the enteral route is unavailable. The stable plasma concentrations afforded by the slow, continuous release of transdermal preparations avoid significant peaks and troughs in plasma concentrations. The favourable pharmacokinetic profile and steady-state kinetics of transdermal administration are useful for opioid analgesics, such as fentanyl, avoiding the nausea and drowsiness associated with a high plasma concentration but maintaining a steady state plasma concentration.

It may take some time before a steady-state plasma concentration is achieved through transdermal administration, and many delivery devices incorporate large amounts of drug in the adhesive layer to provide a loading dose, which reduces this period. At steady state, transdermal delivery has several similarities to intravenous infusion. In contrast to intravenous delivery, on removing the adhesive patch, plasma concentrations may decline relatively slowly because of a depot of drug in the surrounding skin.

Iontophoresis is a technique using the application of an electric current to a transdermal patch to allow charged drug molecules to diffuse through the skin. This allows controlled drug administration (as in a fentanyl patch PCA) and improves the delivery of drugs with poor transdermal absorption.

Inhalation

Drugs are delivered via the inhalational route for their local effects on the lungs, and their systemic effects because of rapid absorption into the bronchial circulation. Drugs acting locally on the bronchial tree are commonly given via this route for bronchodilation or the treatment of inflammatory conditions. Whilst systemic toxicity is reduced, the rich vascular supply to the respiratory tree inevitably leads to systemic absorption.

Inhaled volatile agents are given for systemic effect and are discussed elsewhere. Opioids such as fentanyl and diamorphine may be given as nebulised solutions, but this technique is not routine.

Epidural

Epidural delivery is a common route of administration in anaesthetic practice for central neuraxial effect. The epidural space is highly vascular, and significant amounts of drug may be absorbed systemically, even if inadvertent intravenous administration is avoided. Opioids diffuse across the dura to act on spinal opioid receptors, but much of their action when given via the epidural route is the result of systemic absorption. Complications of this route include epidural haematoma and abscess, inadvertent dural puncture with consequent headache or accidental spinal administration of the drug.

Spinal/Intrathecal (subarachnoid)

When given intrathecally, drugs have free access to the neural tissue of the spinal cord. Small drug doses have profound, rapid effects, an advantage and also a disadvantage of the technique. Protein binding is not a significant factor as CSF protein concentration is relatively low.

Pharmacological variability

Individual responses to medications vary for numerous reasons which require adjustment of drug doses or the use of medications directed at different targets. Causes for individual variable responses may be physiological, pathological or iatrogenic and heritable or acquired.

The changes in drug response with age and in pregnancy are good examples of this. Similarly, the use of concurrent drugs or medications may affect the response to new drugs.

Pathological causes for variability may be acquired (such as obesity) or inherited (such as the variable metabolism seen in mutations of the Cytochrome P450 genes).

The effect of age on pharmacokinetics

There are significant changes in physiology throughout aging, which affects the pharmacokinetics of many medications. Changes in body composition during aging affect the distribution of many drugs, with subsequent, predictable effects on plasma and effect site concentrations, accumulation and onset and offset of action.

The normal ageing process causes a decline in the function of many organs, particularly the kidneys, and therefore drugs dependent on renal clearance may have significantly prolonged effects in the elderly.

The cumulative effects of acquired pathology throughout life can affect the response to various medications.

In the neonatal period, increased total body water and a relatively low proportion of body fat results in high volumes of distribution. Lower concentrations of plasma proteins increase the fraction of unbound, active drug in the plasma. Overall, this results in an increased per-weight dose requirement for most drugs, although those that are highly protein bound may need to be adjusted to account for the increased free drug fraction.

Metabolic pathways and renal elimination are immature in neonates; therefore drugs that are activated by cytochrome P450 are rendered ineffective, and drugs that undergo hepatic clearance, such as midazolam, risk accumulation.

With increasing age there is a general decline in lean body mass and total body water. The proportion of body fat increases in middle age and declines in the elderly. This results in a reduced volume of distribution, thereby increasing plasma concentrations.

Additionally, the age-related decline in renal function results in reduced clearance. The combination of these effects can result in increased plasma concentrations of drugs, requiring dose adjustment.

The combination of increased plasma concentrations with a frailty phenotype and coexistent multisystem decline and development of pathological conditions can result in enhanced response to many medications, necessitating cautious titration, particularly for anaesthetic agents.

The effects of obesity on pharmacokinetics

With increasing total body weight, there is an increase in both lean and fatty mass, although in the obese the majority of the additional weight is due to adipose tissues. This results in an increased volume of distribution for fat-soluble drugs and presents a significant risk of drug accumulation and delayed offset.

Clearance increases linearly with increases in lean body mass, although the excess adiposity of obesity does not reflect any further increase in clearance. Therefore using total body weight for drug dosing may be associated with drug toxicity, and for the majority of drugs, lean body weight is used. The major exceptions to this are suxamethonium and atracurium (dosed by total body weight).

Pharmacogenetics

Pharmacogenetics refers to genetic differences in metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect and adverse effects.

Codeine is an example of the importance of pharmacogenetics. As a prodrug, codeine is metabolised to morphine by the cytochrome P450 system (CYP2D6). There are several common genetic variants of this, resulting in inactivation, slow, rapid or ultra-rapid metaboliser phenotypes. Where administered to an individual with an ultra-rapid phenotype, the plasma concentration of morphine and active metabolites after a dose of codeine can result in opioid toxicity. As the cytochrome P450 oxidases are heavily involved in drug metabolism, these variations can result in altered responses to a large number of drugs processed by this system.

The depolarising muscle relaxant suxamethonium is metabolised by butyrylcholinesterase. Genetic variants of this enzyme may show reduced activity; when an individual is homologous for an inhibited enzyme, the duration of action of suxamethonium is significantly prolonged.

Drug interactions and adverse drug effects

There are three basic types of drug interaction, pharmaceutical, pharmacokinetic and pharmacodynamic.

Pharmaceutical

In pharmaceutical interactions, drugs mixed in the same syringe or infusion bag react chemically, with adverse results which may include neutralisation, hydrolysis, precipitation. For example, mixing suxamethonium with thiopental (pH 10–11) hydrolyses the former, rendering it inactive. Before mixing drugs, data should be sought on their compatibility to avoid this form of interaction.

Pharmacokinetic

Pharmacokinetic interactions occur where coadministration of drugs affects the processes of absorption, distribution, metabolism or elimination. Absorption of a drug, particularly if given orally, may be affected by other drugs because of their action on gastric emptying (see earlier). Interference with protein binding (see earlier) is a common cause of drug interaction. Drug metabolism is discussed in some detail and there are many potential sites in this process where interactions can occur (e.g. competition for enzyme systems, enzyme inhibition or induction).

Pharmacodynamic

Pharmacodynamic interactions are the competing or additive observed effects of coadministered drugs, and are the most common type of interaction in anaesthetic practice. A typical anaesthetic is a series of pharmacodynamic interactions. These may be adverse (e.g. increased respiratory depression with opioids and volatile agents) or advantageous (e.g. reversal of muscle relaxation with neostigmine). An understanding of the many subtle pharmacodynamic interactions in modern anaesthesia accounts for much of the difference in the quality of anaesthesia and recovery associated with the experienced compared with the novice anaesthetist.

Adverse drug reactions

Adverse drug reactions are described as A or B, representing augmented or idiosyncratic reactions, respectively. Type A reactions are related to an increase in the expected pharmacological effect of a drug, which may either relate to the desired effect (e.g. prolonged muscle relaxation) or undesirable effects (e.g. nausea and vomiting from opioids). These are often dose related and are common. Sometimes individual drug variability may result in an increase in the expected drug effect – such as an enhanced codeine effect for fast-metabolising individuals expressing rapid or ultra-rapid CYP450 mutations.

Type B reactions are idiosyncratic and unrelated to the expected properties of a drug. These include immune and idiopathic reactions. Examples include anaphylactoid reactions seen with morphine and atracurium and malignant hyperthermia in susceptible individuals exposed to volatile anaesthetic agents or suxamethonium.