

Clinical pharmacology: the basics

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Abstract

Clinical pharmacology encompasses an understanding of how drugs work and their appropriate use in humans. This chapter gives an overview of the general principles, and subsequent contributions will explore these areas in more detail. Some recent references are included to guide reading around the topics discussed.

Keywords bioavailability; delivery systems; drug monitoring; elimination; half-life; pharmacodynamics; pharmacogenetics; pharmacokinetics; therapeutic index

Pharmacodynamics

The measurement of the effects of drugs on humans (or, in basic pharmacology, an organ system) is termed 'pharmacodynamics'. This term encompasses both the mechanism of action and the end-point (e.g. heart rate, blood pressure).

Receptors

The actions of most drugs are mediated by the binding and interaction of drug molecules with specific molecular substances or macromolecules located on the cell surface, termed 'receptors'. A few receptor sites are intracellular (e.g. steroid receptors). The drug-receptor interaction leads to a molecular change in the receptor, which triggers a chain of events leading to a response. This may be because of a secondary intracellular change mediated by 'second messenger' systems such as G proteins, or because of the change in permeability of an ion channel in the

cell membrane.¹⁻³ Receptors tend to be highly specific, interacting with a limited number of structurally related molecules. There are subgroups of many receptor types, e.g. dopamine 1 and 2, and opioid mu, kappa and delta. For some drugs, the 'receptor' is nonspecific (e.g. an alkylating agent that cross-binds molecules within DNA).

Agonists and antagonists

Agonists are drugs that activate a receptor response. Antagonists are drugs that block receptor response. Examples of such receptor systems include:

- adrenergic (agonist: salbutamol, antagonist: atenolol)
- dopaminergic (agonist: dopamine, antagonist: haloperidol)
- cholinergic (agonist: bethanecol, antagonist: atropine).

Potency

The magnitude of the effect following a drug-receptor interaction usually depends on the dose of drug given; this relationship is commonly expressed in the form of a dose-response curve. Onset of response occurs at a threshold dose. For different drugs with similar actions, use of a dose-response curve allows comparison of:

- potency (the amount of drug necessary to achieve a certain effect)
- ED₅₀ (the dose that produces a 50% response)
- efficacy (the overall effect of a drug).

Potency has little clinical relevance, however, because a drug that is more potent than another may also produce more dose-related adverse effects. It is often possible to use a higher dose of a less potent drug to get the same effect as a more potent drug, sometimes with fewer adverse effects.

Therapeutic index

The therapeutic index (therapeutic ratio) is the ratio between the toxic dose and the therapeutic dose of a drug. The closer this ratio is to 1, the more difficult the drug is to use in clinical practice. The therapeutic index for digoxin, for example, is very low, whereas that for amoxicillin is extremely high. Clinical use of drugs with a narrow therapeutic index has led to the monitoring of drug concentrations in patients – therapeutic drug monitoring – in which the plasma concentration of a drug is measured and the dose adjusted to achieve a desired therapeutic drug concentration (see below).

LD₅₀

In the past, toxicology studies in animals involved measurement of the dose of drug required to kill acutely. The single dose required to kill 50% of a population is called the LD₅₀. This is not a helpful measure in clinical practice, however, and other measures of toxicity are now generally applied, particularly because of animal welfare concerns.

ED₅₀

When a drug is given to an animal or human, it has an effect and elicits a measurable response such as increased intracellular calcium level, reduced blood pressure, or reduced heart rate. A dose-response curve is created by plotting the response on the y axis and the dose of drug on the x axis (usually in log units). The dose at which the response is 50% of the maximal effect is termed the ED₅₀.

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Pharmacokinetics and drug metabolism

The term 'pharmacokinetics' refers to the rate and manner in which drugs are absorbed, distributed, metabolized, and eliminated (termed ADME) within and from the body. Knowledge of drug pharmacokinetics clarifies the relationships between dose, dose frequency, intensity of pharmacological effects, disease, and adverse events.^{4,5}

Absorption and bioavailability

Orally administered drugs must be absorbed from the gut (usually in the upper small bowel, where the surface area is greatest). Not all of an orally administered dose may enter the systemic circulation, however, because of inefficient absorption, or because of metabolism in the gut wall or liver before the drug enters the systemic circulation. This metabolism before a drug reaches the systemic circulation is termed 'first-pass metabolism'. The amount of drug entering the systemic circulation as a proportion of that administered is termed the 'bioavailability'. Bioavailability can be calculated by comparing areas under the plasma concentration–time curves for the same dose given orally and intravenously (intravenous doses are completely 'absorbed' and undergo no first-pass effect). Bioavailability is expressed as a percentage.

It is possible to avoid first-pass metabolism by giving drugs by other routes; for example, sublingual or dermal administration may occasionally be appropriate for nitrates. Alternatively, the oral dose can be increased appropriately.

Some drugs have been pharmaceutically designed to alter their absorption properties. Some are released slowly from tablets – so-called slow-release products. This is often done to lengthen the dosing interval, but may make dose titration more difficult. Others are designed to pass through the small bowel and be released in the large bowel, where they have their effect. This has been done for some ulcerative colitis treatments by synthesizing esters that are broken down by colonic bacterial flora. Alternatively, pH-sensitive coatings can be applied which release the drug as gut pH rises in the colon.

Distribution

To allow simple mathematical modelling of the uptake and distribution of drugs in humans, the body is regarded as a single fluid-filled compartment.

The simplest situation is a drug given intravenously that is distributed throughout the body via the bloodstream.

- Following intravenous injection, the drug passes through the lungs and heart, and then to dependent organs.
- Organs and tissues with the greatest blood supply (e.g. brain, kidneys, liver) are exposed to a greater amount of drug than those with a low blood supply.
- The drug equilibrates with these tissues according to blood supply and its relative water (hydrophilic) or lipid (lipophilic) solubility. As a 'rule of thumb', the more lipophilic the drug, the more of it enters lipid-rich tissues; the less lipophilic the drug, the more remains in the plasma.

The period during which a drug is distributed through body tissues is termed the 'distribution phase'.

Some drugs are bound to plasma proteins. In this state, they are inactive as they cannot interact with receptors. Only free

drug is active. This is important if measurement of the drug's total plasma concentration is assumed to give the concentration of active drug. In conditions such as renal failure, drug–protein binding alters. During dialysis, highly protein-bound drugs are less easily removed. However, protein binding is rarely clinically important, except for some drug interactions.

Apparent volume of distribution (Vd)

Vd is a theoretical volume into which a dose of drug appears to have been dissolved on administration to a patient. It is determined by measuring the plasma concentration during the distribution phase before elimination has occurred ($Vd = D/C$, where D is the total amount of drug in the body and C is the concentration of drug in the plasma). In practice, Vd is determined from a plot of plasma concentration versus time. Knowledge of the Vd is important clinically since it determines how large a loading dose is required of a particular drug to fill up the body and get the drug working optimally.

- Drugs that are highly fat soluble, or taken up rapidly by certain tissues, are removed from the circulation quickly and therefore have a low plasma concentration. As a result, Vd is high – possibly greater than the volume of the patient (e.g. the volume of distribution of tricyclic antidepressants and phenothiazine antipsychotics is several thousand litres).
- For drugs that are water soluble, Vd is low, and more closely similar to plasma volume (e.g. that of ethanol is about two-thirds of body weight).

Elimination

Drugs are eliminated from the body by various processes, of which the most important are renal, biliary, and (for volatile compounds such as anaesthetics) respiratory.

Phase I and phase II metabolism: before elimination can occur, lipid-soluble drugs must be converted into more water-soluble compounds by processes known as phase I and phase II enzymatic metabolism. The most important drug-metabolizing enzymes for phase I metabolism are members of the cytochrome P450 superfamily of haem protein enzymes (e.g. CYP1A2, CYP2D6 and CYP3A4). These enzymes are responsible for the metabolism of a wide variety of drugs. Sulphate, glucuronide and glutathione transferase enzymes are important phase II enzymes. Differences in enzyme activities may have clinical implications.⁶

- In phase I metabolism, reactive groups are introduced into the drug molecule by oxidation, reduction or hydrolysis. Polymorphisms (genetic variations) of these enzymes are common and have important effects on drug metabolism – see pages 355–359.
- In phase II metabolism, these groups undergo conjugation, usually in the liver with glucuronide or sulphate.

Elimination in liver disease: drug-metabolizing enzymes are present in many body tissues, including plasma, but are most active in the liver. Drug metabolism may therefore be impaired in patients with liver disease.

Elimination in renal disease: drug excretion is often reduced in patients with renal impairment; this is particularly important for drugs that are excreted unchanged or have active metabolites.

An example is codeine; this is metabolized to form morphine, which is further metabolized to an active 6-glucuronide compound. Accumulation of this compound can occur in renal failure, leading to excess sedation and respiratory depression.

Effects of other drugs: the activity of drug-metabolizing enzymes in the liver may be increased (induced) or reduced (inhibited) by external factors. Changes in metabolism are particularly important for drugs with a low therapeutic index (e.g. warfarin, theophylline, phenytoin). Common examples of compounds that inhibit and induce drug metabolism are shown in Table 1.

First-order kinetics: in general, the rate at which drugs are metabolized and eliminated from the body is proportional to the blood concentration, and hence to the dose of drug administered. Such drugs are said to obey first-order kinetics. An effective measure of the rate of elimination of such drugs is the plasma half-life ($t_{1/2}$, see below); drugs are considered to be completely eliminated after four to five half-lives.

Zero-order kinetics: occasionally, enzyme metabolism is saturable, i.e. the body is unable to eliminate more than a certain amount of drug over a fixed period of time due to a limiting amount of metabolizing enzyme. Drugs such as phenytoin and alcohol are said to obey zero-order (saturation) kinetics. Unlike drugs obeying first-order kinetics (for which doubling the dose

effectively doubles the plasma concentration), even a small increase in the dose of these drugs produces a disproportionately large increase in plasma concentration that may precipitate toxicity.

Elimination rate constant: drug elimination may be quantified by determining the rate of elimination, described by the elimination rate constant (K). The simplest method to calculate K is from the slope of a natural logarithm plot of the plasma concentration–time curve, which is a straight line. Drug elimination can also be measured in terms of clearance (in a manner analogous to creatinine clearance) as the volume of plasma cleared of drug per unit time.

Half-life: a simpler means of understanding and using these elimination parameters, and of facilitating patient care, is to express the information in terms of $t_{1/2}$. This is defined as the time taken for the plasma concentration of a drug to decrease to 50% of the original value. Thus, if the plasma concentration of a drug decreases from 8 mmol/L to 4 mmol/L in 4 hours, the elimination $t_{1/2}$ of that drug is 4 hours. The $t_{1/2}$ can also be calculated from the equation $t_{1/2} = 0.693/K$. $t_{1/2}$ is clinically important because it enables determination of:

- dosing frequency as drugs with short half-lives need to be given more often. As an approximation, most drugs need to be given at around one to two half-life intervals. (A drug such as digoxin with a $t_{1/2}$ of 36 hours can be given once per day. Theophylline has a short $t_{1/2}$ and is therefore difficult to use in conventional tablets, since as many as 10 doses would be needed each day. The pharmacokinetics of short $t_{1/2}$ drugs may be altered by pharmaceutical means, usually by administering the drug in a slow-release formulation.)
- the time elapsed before a steady-state plasma concentration is reached following repeat dosing (four to five half-lives)
- whether use of a loading dose is appropriate (appropriate when drug action is required before four to five half-lives has elapsed).

However, many drugs exhibit a pharmacological action (pharmacodynamic) that is longer than the elimination $t_{1/2}$, because they produce secondary cellular changes that persist after the drug has gone. There may also be a delay in the onset of effect after the peak blood level, e.g. warfarin, where effect is determined by alterations in clotting factor synthesis.

Pharmacogenetics

Several drug-metabolizing enzymes are subject to genetic variation in activity, and this can lead to large differences in the rate of drug clearance from the plasma, unexpected prolongation of $t_{1/2}$ and increased adverse effects. Pharmacogenetic variations are relatively common and may vary significantly between races.^{7,8} ‘Slow metabolizers’ are more likely to develop adverse effects such as peripheral neuropathy with isoniazid, while ‘fast metabolizers’ may never be able to attain a therapeutic concentration of the drug. Amongst Caucasians, slow metabolizers of a drug such as metoprolol, by the cytochrome p450 isoform CYP2D6, comprise about 8% of the population. These polymorphisms are clinically important; for example, codeine is converted to morphine by CYP2D6 and 8% of the UK population may not get

Commonly used drugs and environmental factors that induce or inhibit drug metabolism

Enzyme-inducing agents

- Carbamazepine
- Phenobarbitone
- Phenytoin
- Rifampicin
- Chronic ethanol consumption
- Smoking
- Barbecued meat
- St John's wort

Enzyme-inhibiting agents

- Cimetidine
- Ciprofloxacin
- Co-trimoxazole
- Erythromycin and clarithromycin
- Ketoconazole and other imidazole antifungals
- Grapefruit juice

Drugs with which these agents commonly interact

- Warfarin
- Carbamazepine
- Cyclosporin
- Phenytoin
- Theophylline
- Low-dose oral contraceptives

All of these drugs have relatively narrow therapeutic ranges.

Table 1

adequate analgesia. Increasing numbers of drugs are recognized to be subject to such variable metabolism, and testing for common genetic polymorphisms is now a routine part of new drug development. This knowledge is also now affecting how some drugs are used. For example mercaptopurine toxicity is linked to its detoxification genotype.⁹

The routine use of pharmacogenetics in clinical practice still seems some way off.¹⁰

Therapeutic drug monitoring

Therapeutic drug monitoring may be required for some drugs with a low therapeutic index in which the relationship between dose and plasma concentration is not easily calculated but for which the plasma level/biological effect is well documented. Usually, this process involves measuring the plasma drug concentration at steady-state (e.g. digoxin, phenytoin). In some circumstances, the trough plasma concentration of the drug (i.e. the concentration immediately before the next dose is administered; e.g. vancomycin) or the peak plasma concentration (e.g. gentamicin) may need to be measured. Dosing interval and $t_{1/2}$ affect the amount of drug in the body at any one time, and knowledge of these factors enables implementation of logical dosing regimens.

Drug interactions

Interactions between drugs may result in changes in their pharmacokinetics (pharmacokinetic interaction) or an increase or decrease in their biological effect (pharmacodynamic interaction).

Pharmacokinetic interactions

Pharmacokinetic interactions most commonly involve changes in metabolism in the liver (enzyme inhibition – see above) or excretion by the kidneys. Rarely, protein-binding displacement causes a change in distribution.

Pharmacodynamic interactions

In pharmacodynamic interactions, different drugs act at different receptor systems to produce, most commonly, an increased biological effect. A useful pharmacodynamic interaction is the anti-hypertensive effect of concurrent ACE inhibitor and calcium channel antagonist therapy in hypertensive patients. This interaction may be detrimental, however, when the same drugs cause hypotensive blackouts in patients treated for angina.

Adverse drug reactions

Adverse drug reactions are common and give rise to considerable morbidity and mortality. On an average general medical take of 30 patients it is likely that two patients will have presented as a direct result of adverse drug effects.¹¹ Adverse drug reactions can be classified in a number of ways, but in essence, harm results from:

- toxic effects when the concentration of drug is too high, e.g. respiratory depression occurring in a patient receiving morphine in whom renal failure has resulted in accumulation of morphine and its active metabolites
- collateral effects when the drug is present at the desired concentration but unintended 'side effects' arise, e.g. diclofenac causing gastrointestinal bleeding

- hypersusceptibility to a drug, e.g. an allergic reaction to penicillin.

See pages 364–368 for further information.

Pharmacovigilance

Pharmacovigilance is the branch of pharmaco-epidemiology that concentrates on the detection of adverse drug reactions. Adverse drug reactions often mimic common disease states, and uncommon adverse drug reactions may be difficult to detect unless they are severe or are clearly temporally related to a specific medication. In the UK, there are three types of pharmacovigilance study.^{12,13}

- The Yellow Card reporting system is a spontaneous-reporting alerting system that may be used as a hypothesis-generating process. It relies on healthcare professionals reporting any adverse event that they suspect may be caused by a medication. There is no requirement for proof.
- Prescription Event Monitoring is a systematic cohort approach that may also act as a hypothesis-generating and testing process. It is typified by the Green Form in the UK, and is based on the monitoring of dispensed prescriptions for new drugs via a central agency.
- The third technique involves hypothesis testing, when previous data have suggested that a drug may be responsible for a particular adverse event. Hypothesis testing usually involves case-control studies. Randomized clinical studies and cohort studies are usually less efficient, because large numbers of patients are required to detect rare events.

Delivery systems

For most drugs, there is a direct relationship between pharmacological response and concentration at the receptor; thus, to be biologically active, the drug must gain access to the systemic circulation and then come into contact with the receptor. Plasma drug concentration depends on both drug kinetics and the design of the drug delivery system.

Oral administration

The most commonly used delivery systems involve absorption of drug from the gastrointestinal tract following buccal, sublingual, rectal or, most often, oral administration. Commonly encountered oral forms include:

- solutions
- suspensions
- capsules
- tablets
- coated tablets
- modified-release tablets.

The time taken for the drug to appear in the systemic circulation following oral administration increases in approximately the same order.

Tablets are the most common delivery system. They have the advantages of convenience and accuracy of dose. Tablets contain many chemicals apart from the active drug – these are the 'excipients', which include taste, colour and other formulation materials.

Coated tablets – it is possible to alter the delivery and apparent kinetics of drugs by changing the dissolution characteristics of

tablets. Thus, a tablet may be enteric-coated to prevent breakdown in the stomach, ensuring that it remains intact until it reaches the small bowel. This approach is commonly used to protect drugs that are destroyed by gastric acid (e.g. omeprazole).

Modified-release tablets – the excipients of tablets may be modified to improve drug delivery by controlling the rate, amount, and duration of drug release over a 24-hour period. This approach is used for drugs with a short $t_{1/2}$, which require frequent dosing to maintain therapeutic levels (e.g. theophylline, verapamil).

Pro-drugs are inactive compounds that are activated by biological fluids or metabolizing enzymes following administration (e.g. enalapril is converted to its active form enalaprilat). Their effect is usually similar to other drugs in the same class.

Sublingual and buccal administration

These routes are increasingly used as tools to deliver drugs more rapidly than orally but without the need for injection. Passage across the mucosa is rapid for some compounds (e.g. nitrates) and avoids first-pass metabolism.

Inhalation

Inhaled drugs generally have less systemic availability so allow smaller doses to be given for a direct effect on the lung. Some absorption does occur, and may be clinically important in causing adverse effects in the case of high-potency steroids, or nebulized β -agonists.

Intravenous administration

Intravenous administration is most commonly used when rapid onset of action and careful control of plasma levels are required. Drugs may be given as a:

- bolus injection
- slow infusion
- continuous infusion.

Slow infusion is used when excessively high transient plasma levels are undesirable (e.g. phenytoin).

Continuous infusion is used when the drug has a short $t_{1/2}$ or when its therapeutic index is narrow and sustained controlled blood levels are required.

Clinical trials

Clinical trials are discussed on pages 369–376 and 377–381.

Concordance and compliance

If a drug is to achieve the desired therapeutic effect, it is necessary for the patient to take their medical therapy. Concordance, formerly called compliance, is the term that is used to describe the extent to which patients follow the course of treatment. Factors believed to be important in ensuring patient concordance include the complexity of the therapeutic regimen, patients' understanding of their disease, and the need for and benefits of treatment. Careful studies have shown that 33% of patients on long-term therapy show complete concordance while 66% are at least reasonably concordant (i.e. missing occasional doses

at worst). About one third of patients take their treatment in a completely haphazard way, if at all. Surprisingly, studies have shown that concordance with life-saving therapy, such as immunosuppression or cancer chemotherapy, is no better. This should be born in mind when extrapolating clinical trial data, in which concordance is carefully monitored. ♦

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