Part 1

Principles of clinical pharmacology

Pharmacodynamics and pharmacokinetics

Clinical scenario
A 50-year-old obese man with type 2 diabetes, hypertension and hyperlipidaemia has made arrangements to see his general practitioner to review his medications. He is on three different drugs for his diabetes, four different anti-hypertensives, a statin for his cholesterol and a dispersible aspirin. These medications have been added over a period of 2 years despite him not having any symptoms and he feels that if anything they are giving him symptoms of fatigue and muscle ache. He has also read recently that aspirin may actually be bad for patients with diabetes. He is keen to know why he is on so many medications, if the way he is feeling is due to the medications and whether they are interfering with the action of each other. What knowledge might help the general practitioner deal with this?

KEY POINTS – WHAT IS PHARMACODYNAMICS AND PHARMACOKINETICS?

- The variability in the relationship between dose and response is a measure of the sensitivity of a patient to a drug. This has two components: dose – concentration and concentration – effect.
- The latter is termed pharmacodynamics. The description of a drug concentration profile against time is termed pharmacokinetics.
- In simple terms pharmacodynamics is what the drug does to the individual taking it and pharmacokinetics what the individual does to the drug.
- Clinical pharmacology seeks to explore the factors that underlie variability in pharmacodynamics and pharmacokinetics for the optimization of drug therapy in individual patients.

Introduction

A basic knowledge of the mechanism of action of drugs and how the body deals with drugs allows the clinician to prescribe safely and effectively. Prior to the twentieth century prescribing medication was based on intelligent observation and folklore with medical practices depending largely on the administration of mixtures of natural plant or animal substances. These preparations contained a number of pharmacologically active agents in variable amounts (e.g. powdered bark from the cinchona tree, now known to contain quinine, being used by natives of Peru to treat ‘fevers’ caused by malaria).

During the last 100 years an increased understanding has developed of biochemical and pathophysiological factors that influence disease. The chemical synthesis of agents with well-characterised and specific actions on cellular mechanisms has led to the introduction of many powerful and effective drugs. Additionally, advances in the detection of these compounds in body fluids have facilitated investigation into the relationships between the dosage regimen, the profile of drug concentration against time in body fluids, notably the plasma, and corresponding profiles of clinical effect. Knowledge of this concentration–effect relationship, and the factors that influence drug concentrations, underpin early stages of the drug development process.
More recently the development of genomics and proteomics has provided additional insights and opportunities for drug development with new and more specific targets. Such knowledge will replace the concept of one drug and/or one dose fitting all.

**Principles of drug action (pharmacodynamics)**

Pharmacological agents are used in therapeutics to:

1. **Alleviate symptoms**, for example:
   - Paracetamol for pain
   - GTN spray for angina
2. **Improve prognosis** – this can be measured in number of different ways – usually measured as a reduction in morbidity or mortality, for example:
   - Prevent or delay end stage consequences of disease, e.g. anti-hypertensive medication and statins in cardiovascular disease, levodopa in Parkinson’s disease
   - Replace deficiencies, e.g. levothyroxine in hypothyroid
   - Cure disease, e.g. antibiotics, chemotherapy

Some drugs will both alleviate symptoms and improve prognosis, e.g. beta-blockers in ischaemic heart disease. If a prescribed drug is doing neither one must question the need for its use and stop it. Even if there is a clear indication for use the potential for side effects and interactions with any other drugs the patient is on also needs to be taken into account.

**Action on an enzyme**

Enzymes, like receptors, are protein macromolecules with which substrates interact to produce activation or inhibition. Drugs in common clinical use which exert their effect through enzyme action generally do so by inhibition, for example:

1. Aspirin inhibits platelet cyclo-oxygenase
2. Ramipril inhibits angiotensin-converting enzyme

Drug receptor antagonists and enzyme inhibitors can act as competitive, reversible antagonists or as non-competitive, irreversible antagonists. Effects of competitive antagonists can be overcome by increasing the dose of endogenous or exogenous agonists, while effects of irreversible antagonists cannot usually be overcome resulting in a longer duration of the effect.

**Action on membrane ionic channels**

The conduction of impulses in nerve tissues and electromechanical coupling in muscle depend on the movement of ions, particularly sodium, calcium and potassium, through membrane channels. Several groups of drugs interfere with these processes, for example:

1. Nifedipine inhibits the transport of calcium through the slow channels of active cell membranes
2. Furosemide inhibits Na/K/Cl co-transport in the ascending limb of the loop of Henle

**Cytotoxic actions**

Drugs used in cancer or in the treatment of infections may kill malignant cells or micro-organisms. Often the mechanisms have been defined in terms of effects on specific receptors or enzymes. In other cases chemical action (alkylation) damages DNA or other macromolecules and results in cell death or failure of cell division.

A **partial agonist** stimulates the receptor to a limited extent, while preventing any further stimulation by naturally occurring agonists, e.g. aripiprazole at the D2 and 5-HT1A receptors.

The biochemical events that result from an agonist-receptor interaction to produce an effect are complex. There are many types of receptors and in several cases subtypes have been identified which are also of therapeutic importance, e.g. α and β-adrenoceptors and nicotinic and muscarinic cholinergic receptors.
Dose–response relationship

Dose–response relationships may be steep or flat. A steep relationship implies that small changes in dose will produce large changes in clinical response or adverse effects, while flat relationships imply that increasing the dose will offer little clinical advantage (Figure 1.1).

In clinical practice the maximum therapeutic effect may often be unobtainable because of the appearance of adverse or unwanted effects: few, if any, drugs cause a single pharmacological effect.

The concentration–adverse response relationship is often different in shape and position to that of the concentration–therapeutic response relationship. The difference between the concentration that produces the desired effect and the concentration that causes adverse effects is called the therapeutic index and is a measure of the selectivity of a drug (Figure 1.2).

The shape and position of dose–response curves for a group of patients is variable because of genetic, environmental and disease factors. However, this variability is not solely an expression of differences in response to drugs. It has two important components: the dose–plasma concentration relationship and the plasma concentration–effect relationship.

Dose → Concentration → Effect

With the development of specific and sensitive chemical assays for drugs in body fluids, it has been possible to characterise dose–plasma concentration relationships so that this component of the variability in response can be taken into account when drugs are prescribed for patients with various disease states. For drugs with a narrow therapeutic index it may be necessary to measure plasma concentrations to assess the relationship between dose and concentration in individual patients (see Chapter 20 Therapeutic Drug Monitoring).

Principles of pharmacokinetics

Absorption

Drug absorption after oral administration has two major components: absorption rate and bioavailability. Absorption rate is controlled partially by the physicochemical characteristics of the drug but in many cases is modified by the formulation. A reduction in absorption rate can lead to a smoother concentration–time profile with a lower potential for concentration-dependent adverse effects and may allow less frequent dosing.

Bioavailability is the term used to describe the fraction of the dose that is absorbed into the systemic circulation. It can range from 0 to 100% and depends on a number of physicochemical and clinical factors. Low bioavailability may occur if the drug has low solubility or is destroyed by the acid in the stomach. Changing the formulation can affect the bioavailability of a drug and it can also be altered by food or the co-administration of other drugs. For example,
antacids can reduce the absorption of quinolone antibiotics, such as ciprofloxacin, by binding them in the gut. Other factors influencing bioavailability include metabolism by gut flora, the intestinal wall or the liver.

First-pass metabolism refers to metabolism of a drug that occurs en route from the gut lumen to the systemic circulation. For the majority of drugs given orally, absorption occurs across the portion of gastrointestinal epithelium that is drained by veins forming part of the hepatoportal system. Consequently, even if they are well absorbed, drugs must pass through the liver before reaching the systemic circulation. For drugs that are susceptible to extensive hepatic metabolism, a substantial proportion of an orally administered dose can be metabolised before it ever reaches its site of pharmacological action, e.g. insulin metabolism in the gut lumen is so extensive that it renders oral therapy impossible.

The importance of first-pass metabolism is twofold:

1. It is one of the reasons for apparent differences in drug bioavailability between individuals. Even healthy people show considerable variation in liver metabolising capacity.
2. In patients with severe liver disease first-pass metabolism may be dramatically reduced, leading to the appearance of greater amounts of active drug in the systemic circulation.

Clinical relevance of volume of distribution

Knowledge of volume of distribution ($V_D$) can be used to determine the size of a loading dose if an immediate response to treatment is required. This assumes that therapeutic success is closely related to the plasma concentration and that there are no adverse effects if a relatively large dose is suddenly administered. It is sometimes employed when drug response would take many hours or days to develop if the regular maintenance dose was given from the outset, e.g. digoxin.

In practice, weight is the main determinant to calculating the dose of a drug where there is a narrow therapeutic index.

Plasma protein binding

In the blood, a proportion of a drug is bound to plasma proteins – mainly albumin (acidic drugs) and $\alpha_1$-acid glycoprotein (basic drugs). Only the unbound, or free, fraction distributes because the protein-bound complex is too large to pass through membranes. It is the unbound portion that is generally responsible for clinical effects – both the target response and the unwanted adverse effects. Changes in protein binding (e.g. resulting from displacement interactions) generally lead to a transient increase in free concentration but are rarely clinically relevant. However, a lower total concentration will be present and the measurement might be misinterpreted if the higher free fraction is not taken into account. This is a common problem with the interpretation of phenytoin concentrations, where free fraction can range from 10% in a normal patient to 40% in a patient with hypoalbuminaemia and renal impairment.

Clearance

Clearance is the sum of all drug-eliminating processes, principally determined by hepatic metabolism and renal excretion. It can be defined as the theoretical volume of fluid from which a drug is completely removed in a given period of time.

When a drug is administered continuously by intravenous infusion or repetitively by mouth, a balance is eventually achieved between its input (dosing rate) and its output (the amount eliminated over a given period of time). This balance gives rise to a constant amount of drug in the body which depends on the dosing rate and clearance. This amount is reflected in the plasma or serum as a steady-state
concentration (C_{ss}). A constant rate intravenous infusion will yield a constant C_{ss}, while a drug administered orally at regular intervals will result in fluctuation between peak and trough concentrations (Figure 1.3).

Clearance depends critically on the efficiency with which the liver and/or kidneys can eliminate a drug; it will vary in disease states that affect these organs, or that affect the blood flow to these organs. In stable clinical conditions, clearance remains constant and is directly proportional to dose rate. The important implication is that if the dose rate is doubled, the C_{ss \text{average}} doubles; if the dose rate is halved, the C_{ss \text{average}} is halved for most drugs. In pharmacokinetic terms this is referred to as a first-order or linear process, and results from the fact that the rate of elimination is proportional to the amount of drug present in the body.

**Single intravenous bolus dose**

A number of other important pharmacokinetic principles can be appreciated by considering the concentrations that result following a single intravenous bolus dose (see Figure 1.4) and through a number of complex equations the time at which steady state will be achieved after starting a regular treatment schedule or after any change in dose can be predicted.

As a rule, in the absence of a loading dose, steady state is attained after four to five half-lives (Figure 1.5).

Furthermore, when toxic drug levels have been inadvertently produced, it is very useful to estimate how long it will take for such levels to reach the therapeutic range, or how long it will take for the entire drug to be eliminated once the drug has been stopped. Usually, elimination is effectively complete after four to five half-lives (Figure 1.6).

The elimination half-life can also be used to determine dosage intervals to achieve a target concentration–time profile. For example, in order to obtain a gentamicin peak of 8 mg/L and a trough of 0.5 mg/L in a patient with an elimination half-life of 3 hours, the dosage interval should be 12 hours. (The concentration will fall from 8 mg/L to 4 mg/L in 3 hours, to 2 mg/L in 6 hours, to 1 mg/L in 9 hours and to 0.5 mg/L in 12 hours.) However, for many drugs, dosage regimens should be designed to maintain concentrations within a range that avoids high (potentially toxic) peaks or low, ineffective troughs. Excessive fluctuations in the concentration–time profile can be prevented by giving the drug at intervals of less than one half-life or by using a slow-release formulation.
Pharmacodynamics and pharmacokinetics

Phenytoin, alcohol and heparin. When the enzymes responsible for metabolism reach a point of saturation, the rate of elimination, in terms of amount of drug eliminated in a given period of time, does not increase in response to an increase in concentration (or an increase in the amount of drug in the body) but becomes constant. This gives rise to non-linear or zero-order kinetics.

The clinical relevance of non-linear kinetics is that a small increase in dose can lead to a large increase in concentration. This is particularly important when toxic side effects are closely related to concentration, as with phenytoin.

Principles of drug elimination

Drug metabolism

Drugs are eliminated from the body by two principal mechanisms: (i) liver metabolism and (ii) renal excretion. Drugs that are already water-soluble are generally excreted unchanged by the kidney. Lipid-soluble drugs are not easily excreted by the kidney because, following glomerular filtration, they are largely reabsorbed from the proximal tubule. The first step in the elimination of such lipid-soluble drugs is metabolism to more polar (water-soluble) compounds. This is achieved mainly in the liver, but can also occur in the gut and may contribute to first-pass elimination. Metabolism generally occurs in two phases:

**Phase 1** – Mainly oxidation, but also reduction or hydrolysis to a more polar compound: Oxidation can occur in various ways at carbon, nitrogen or sulphur atoms and N- and O-dealkylation. These reactions are catalysed by the cytochrome P450-dependent system of the endoplasmic reticulum. Knowledge of P450, which exists as a superfamily of similar enzymes (isoforms), has increased greatly recently and is divided into a number of families and subfamilies. Although numerous P450 isoforms are present in human tissue, only a few of these have a major role in the metabolism of drugs. These enzymes, which display distinct but overlapping substrate specificity, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Induction or inhibition of one or more of these enzymes may form the basis of clinically relevant drug interactions. Phase 1 metabolites usually have only minor structural differences from the parent drug,
but may exhibit totally different pharmacological actions. For example, the metabolism of azathioprine produces the powerful antimetabolite 6-mercaptopurine.

**Phase 2 – Conjugation usually by glucoronidation or sulphation to make the compound more polar:** This involves the addition of small endogenous molecules to the parent drug, or to its phase 1 metabolite, and almost always lead to abolition of pharmacological activity. Multiple forms of conjugating enzymes are also known to exist, although these have not been investigated to the same extent as the P450 system.

**Metabolic drug interactions**

The wide range of drugs metabolised by the P450 system provides the opportunity for interactions of two types, namely enzyme induction and inhibition.

<table>
<thead>
<tr>
<th>Clinical scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 24-year-old woman goes to a family planning clinic for advice about contraception. The patient has a history of epilepsy which is stable on carbamazepine 200 mg bd. What options are available to the general practitioner?</td>
</tr>
</tbody>
</table>

**Induction**

Enzyme induction, which may be defined as the increase in amount and activity of drug-metabolising enzymes, is a consequence of new protein synthesis resulting from prolonged exposure to the inducing drug. While a drug may induce its own metabolism, it can also accelerate the metabolism and clearance of unrelated compounds. Many compounds are known to act as enzyme inducers in animals at toxicological dose levels, but relatively few drugs produce clinically significant induction in humans when used at therapeutic dose levels. For practical purposes anticonvulsants (carbamazepine, phenytoin) and rifampicin are the most potent enzyme inducers in clinical use and have produced numerous clinically significant drug interactions, related primarily to increases in the metabolism of CYP2C9, CYP2C19 and CYP3A4 substrates (including for example oestrogen and progesterone, the constituents of a combined oral contraceptive pill). Enzyme induction is not, however, limited to administration of prescription drugs. St John’s wort, a herbal remedy, can also cause enzyme induction as can cigarette smoking (induction of CYP1A2 substrates, e.g. theophylline) and ethanol (induction of CYP2E1 but unlikely to be clinically relevant).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A 58-year-old man with chronic obstructive pulmonary disease is admitted to hospital with an infective exacerbation. He is on three different inhalers and additionally takes simvastatin for hypercholesterolaemia. He is allergic to penicillin. The admitting doctor prescribes nebulised salbutamol, prednisolone and clarithromycin along with the patient’s usual medications. The next day the patient complains of general aches and pains. Could this be due to a drug interaction?</td>
</tr>
</tbody>
</table>

**Inhibition**

Concurrently administered drugs can also lead to inhibition of enzyme activity, with many P450 inhibitors showing considerable isoform selectivity. Some of the most clinically relevant inhibitors are listed in Table 1.1, together with the isoform inhibited. In some cases this can lead to potentially dangerous adverse events, e.g. ketoconazole decreases the metabolism of the CYP3A4 substrate, terfenadine, leading to QT interval prolongation and torsades de pointes.

As with induction, P450 inhibition is not limited to drug administration. Grapefruit juice is an inhibitor of CYP3A4 activity and produces clinically significant interactions with a number of drugs, including midazolam, simvastatin and terfenadine. This type of information, together with some knowledge of the enzymes involved in a particular drug’s clearance, makes it much easier to understand and predict drug interactions.

Clearly, pronounced enzyme inhibition, which may result in plasma concentrations of the inhibited
Pharmacodynamics and pharmacokinetics

Drug being many times higher than intended, can be a major safety issue. For example, co-administration of ketoconazole or ritonavir with the hypnotic drug midazolam increases the midazolam plasma exposure (AUC – area under the curve) by 15–20 times, a situation which should be avoided.

Genetic factors in metabolism

The rate at which healthy people metabolise drugs is variable. Although part of this variability is a consequence of environmental factors, including the influence of inducers and inhibitors, the main factor contributing to interindividual variability in metabolism is the underlying genetic basis of the drug-metabolising enzymes. Although there is probably a genetic component in the control of most P450 enzymes, some enzymes (e.g. CYP2C19 and CYP2D6) actually show genetic polymorphism. This results in distinct subpopulations of poor and extensive metabolisers, where the poor metabolisers are deficient in that particular enzyme. There are a number of enzymes under polymorphic control and some clinically important examples are shown in Table 1.2. As with enzyme inhibition, genetic polymorphism is primarily a concern for drugs that have a narrow therapeutic index and that are metabolised largely by a single polymorphic enzyme. In such cases, the phenotype of the patient should be determined and lower doses of the drug used, or alternative therapy should be considered.

Renal excretion

Three processes are implicated in renal excretion of drugs:

1. **Glomerular filtration**: This is the most common route of renal elimination. The free drug is cleared by filtration and the protein-bound drug remains in the circulation where some of it dissociates to restore equilibrium.

2. **Active secretion in the proximal tubule**: Both weak acids and weak bases have specific secretory sites in proximal tubular cells. Penicillins are eliminated by this route, as is about 60% of procainamide.

3. **Passive reabsorption in the distal tubule**: This occurs only with un-ionised, i.e. lipid-soluble, drugs. Urine pH determines whether or not weak acids and bases are reabsorbed, which in turn determines the degree of ionisation.

If renal function is impaired, for example by disease or old age, then the clearance of drugs that normally undergo renal excretion is decreased.

### Table 1.2 Major enzymes displaying genetic polymorphism.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Typical substrates</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>(S)-Mephenytoin, diazepam, omeprazole</td>
<td>About 2–5% of white people are poor metabolisers, but 18–23% of Japanese people have this phenotype</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Propafenone, flecainamide, desipramine</td>
<td>About 7% of white people are poor metabolisers, but this frequency is only about 2% in black Americans and &lt;1% in Japanese/Chinese</td>
</tr>
<tr>
<td>N-Acetyl-transferase</td>
<td>Hydralazine, sulphonamides, isoniazid, procarbazine</td>
<td>About 50% of white people are slow acetylators</td>
</tr>
</tbody>
</table>