CLINICAL PHARMACOLOGY AND THERAPEUTICS

Lecture Notes

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10th Edition

WILEY Blackwell

Clinical Pharmacology and Therapeutics

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Preface

The successful practice of Medicine is predicated upon the ability to use drugs safely and effectively. This ability can be difficult to acquire and needs to be maintained as the range of drugs available to alleviate symptoms and to treat disease is constantly growing. As our understanding of the genome, and of the molecular basis of disease has increased, the development of new drugs with novel mechanisms of action has accelerated, expanding the available pharmacopeia for clinicians from all disciplines and therapeutic areas.

As our knowledge evolves, so must our textbooks. This tenth edition of Lecture Notes in Clinical Pharmacology has been extensively revised, refreshed and updated to provide the reader with an authoritative and modern insight into the use of drugs in the treatment of human disease.

Although the range of drugs available has expanded hugely since the first edition of this book was published almost 40 years ago, in preparing this text we continue to be guided by the principles established in that edition: we have retained a clear focus on practical elements and clinical relevance throughout, in order to maximise utility for the student or practising clinician. Rather than indulgence in exhaustive detail, we have chosen to set out concisely and with clarity the principles which guide clinicians in their choices and have made use of illustrative examples from scenarios commonly encountered on wards and in clinics. In doing so, we hope to provide the reader with an accessible and helpful guide which imparts a useful understanding of not only how, but also when to use drugs.

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Part 1

Principles of clinical pharmacology

1

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?

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.

KEY POINTS – 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 (pharmacokinetics) and concentration–effect (pharmacodynamics)**
- **Pharmacokinetics describes the processes of drug absorption, distribution, metabolism and excretion**
- **Clinical pharmacology seeks to explore the factors that underlie variability in pharmacodynamics and pharmacokinetics for the optimization of drug therapy in individual patients**

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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 a 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.

Mechanism of drug action

Action on a receptor

A receptor is a specific macromolecule, usually a protein, situated either in cell membranes or within the cell, to which a specific group of ligands, drugs or naturally occurring substances (such as neurotransmitters or hormones) can bind and produce pharmacological effects. There are three types of ligands: agonists, antagonists and partial agonists.

An **agonist** is a substance that stimulates or activates the receptor to produce an effect, e.g. salbutamol at the β_2-receptor.

An **antagonist** prevents the action of an agonist but does not have any effect itself, e.g. losartan at the angiotensin II receptor.

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.

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.

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.

$$\text{Dose} \rightarrow \text{Concentration} \rightarrow \text{Effect}$$

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 Section 'Therapeutic drug monitoring' later).

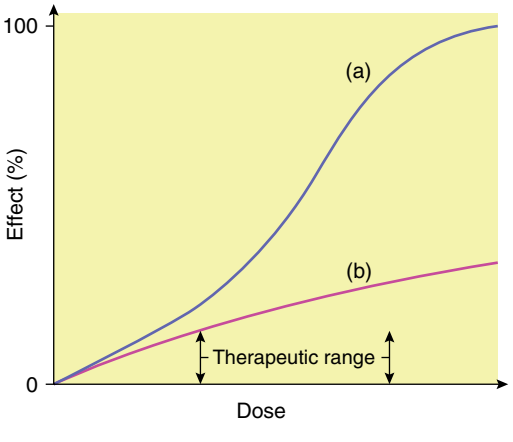

Figure 1.1 Schematic examples of a drug (a) with a steep dose– (or concentration–) response relationship in the therapeutic range, e.g. warfarin an oral anticoagulant; and (b) a flat dose– (or concentration–) response relationship within the therapeutic range, e.g. thiazide diuretics in hypertension.

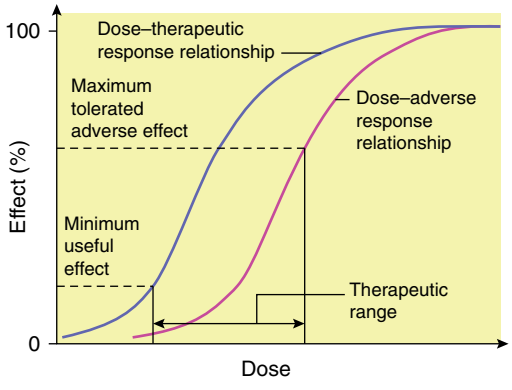

Figure 1.2 Schematic diagram of the dose–response relationship for the desired effect (dose–therapeutic response) and for an undesired adverse effect. The therapeutic index is the extent of displacement of the two curves within the normal dose range.

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 oral 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. Other drugs which undergo extensive hepatic metabolism include propranolol, lidocaine and morphine.

First-pass metabolism has several clinical implications:

1. The appropriate route has to be selected for a drug in order to obtain its clinical effect
2. It accounts for the variability in drug bioavailability between individuals
3. Liver disease can reduce the first-pass effect and result in an increase in bioavailability. This is discussed in greater detail later in this section.

Distribution

Once a drug has gained access to the bloodstream, it begins to distribute to the tissues. The extent of this distribution depends on a number of factors including plasma protein binding, lipid solubility and regional blood flow. The volume of distribution, V_D, is the *apparent volume* of fluid into which a drug distributes based on the *amount* of drug in the body and the *measured concentration* in the plasma or serum. If a drug was wholly confined to the plasma, V_D would equal the plasma volume – approximately 3 L in an adult. If, on the other hand, the drug was distributed throughout the body water, V_D would be approximately 42 L. In reality, drugs are rarely distributed into physiologically relevant volumes. If most of the drug is bound to tissues, the plasma concentration will be low and the apparent V_D will be high, while high plasma protein binding will tend to maintain high concentrations in the blood and a low V_D will result. For the majority of drugs, V_D depends on the balance between plasma binding and sequestration or binding by various body tissues, for example, muscle and fat. Volume of distribution can therefore vary considerably.

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 α_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

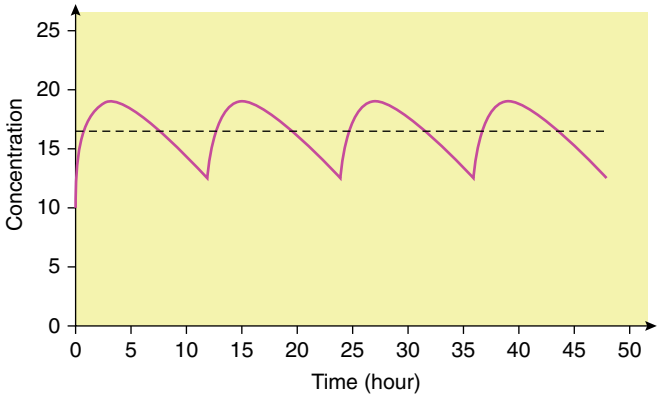

Figure 1.3 Steady-state concentration–time profile for an oral dose (—) and a constant rate intravenous infusion (- - - -).

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 $Css_{average}$ doubles: if the dose rate is halved, the $Css_{average}$ 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).

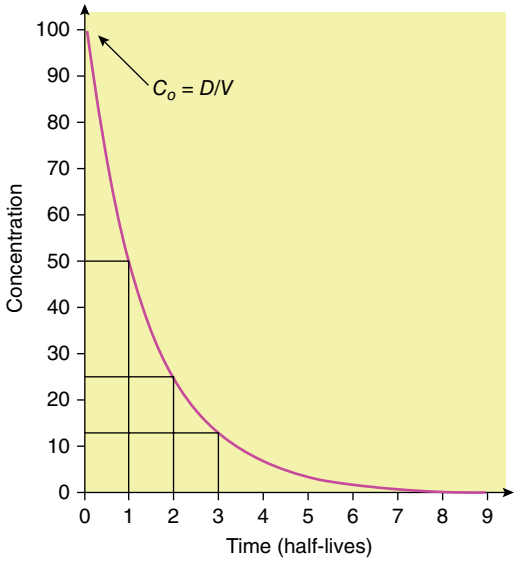

Figure 1.4 Plot of concentration versus time after a bolus intravenous injection. The intercept on the y-(concentration) axis, C_0, is the concentration resulting from the instantaneous injection of the bolus dose.

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 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

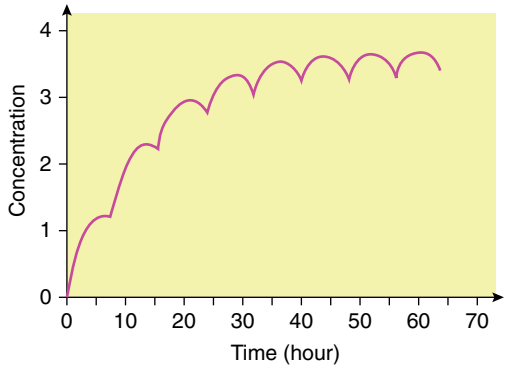

Figure 1.5 Plot of concentration versus time illustrating the accumulation to steady state when a drug is administered by regular oral doses.

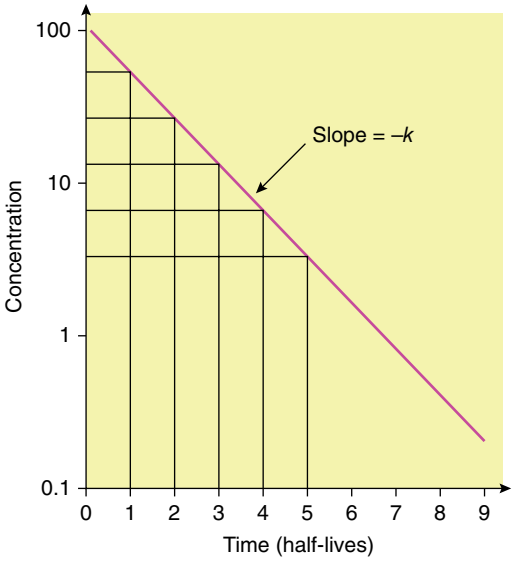

Figure 1.6 Semi-logarithmic plot of concentration versus time after a bolus intravenous injection. The slope of this line is –k; the elimination rate constant and the elimination half-life of the drug can be determined from such a plot by noting the time at which the concentration has fallen to half its original value.

the drug at intervals of less than one half-life or by using a slow-release formulation.

Linear versus non-linear kinetics

As previously mentioned, most drugs display first-order kinetics where the rate of elimination is proportional to the amount of drug in the body. However, drugs such as ethanol, phenytoin and heparin have zero-order kinetics. Here, a constant amount of drug is eliminated per unit time, independent of plasma drug concentration. This occurs when the enzymes responsible for metabolism become saturated and the rate of elimination does not increase in response to an increase in concentration (or an increase in the amount of drug in the body) but becomes constant.

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.

Clinical scenario

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?

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).

KEY POINTS - ENZYME INDUCTION AND INHIBITION

Enzyme induction produces clinical changes over days or weeks, but the effects of enzyme inhibition are usually observed immediately. In most circumstances, these changes are manifest as:

- **Therapeutic failure resulting from induction**
- **Adverse effects resulting from inhibition**

Clinical relevance occurs when drug therapy needs to be altered to avoid the consequences of the drug interaction and this is most common and most serious in compounds that have a narrow therapeutic index.

Clinical scenario

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?

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.

Table 1.1 P450 inhibitors involved in drug interactions.

Major human P450s	Typical inhibitors
CYP1A2	Furafylline, fluvoxamine, ciprofloxacin
CYP2C9	Fluconazole, ketoconazole, sulfaphenazole
CYP2C19	Omeprazole, ketoconazole, cimetidine
CYP2D6	Quinidine, fluoxetine, ritonavir
CYP2E1	Disulfiram
CYP3A4	Ketoconazole, itraconazole, ritonavir, clarithromycin, diltiazem

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 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.

Table 1.2 Major enzymes displaying genetic polymorphism.

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

If renal function is impaired, for example, by disease or old age, then the clearance of drugs that normally undergo renal excretion is decreased. This is discussed in more detail later in this section.

Clinical pharmacokinetics: dosage individualisation

Clinical scenario

A 76-year-old man has been referred with sepsis probably secondary to a urinary tract infection. He is unwell and the hospital guidelines suggest giving him gentamicin. He has a past history of renal impairment which has been stable for some time. What information do you need to know and what dose of gentamicin would you give?

KEY POINTS

- There a number of factors that contribute to a lack of therapeutic effect of a dosed drug in an individual
- Blood monitoring of drug levels is a useful way of ensuring maximum benefit whilst minimising the risk of complications of a particular drug
- Therapeutic drug monitoring is most useful for drugs such as digoxin, phenytoin and gentamicin which have a narrow therapeutic index

Introduction

There are various reasons why a prescribed dose of drug leads to a different plasma drug concentration and therefore clinical effect. These include:

- Individual differences in absorption, first-pass metabolism, volume of distribution and clearance
- Altered pharmacokinetics because of gastrointestinal, hepatic or renal disease
- Drug interactions
- Poor adherence to therapy

For most drugs there is an accepted 'target' range, i.e. a range of concentrations below which the drug is usually ineffective and above which it is usually toxic. In order to maintain drug concentrations within this range, knowledge about factors that influence the relationships between drug dose and blood concentration is used to design dosage regimens. Dosage adjustments based on age, renal function, hepatic function or other drug therapies are often recommended, especially for drugs with a narrow therapeutic index. For example, the initial dose of gentamicin, a renally cleared antibiotic, is based on the patient's renal function. As a consequence of an interaction that increases digoxin concentrations, the dose of digoxin is usually halved when amiodarone is added to a patient's therapy.

Therapeutic drug monitoring

In many cases it is relatively easy to evaluate the pharmacological effects of a drug by clinical observation, and initial dosage regimens can be modified to increase the therapeutic effect or to eliminate unwanted effects. Measurement of drug concentrations in blood can be performed to help with diagnosis or to optimise therapy for those drugs where response (therapeutic or toxic effects) cannot be readily evaluated from clinical observation alone. Examples of drugs where monitoring can usefully aid clinical judgement, together with target ranges, are shown in Table 1.3.

As a result of pharmacokinetic and pharmacodynamic variability, the following factors should be considered when interpreting drug concentration measurements:

1. Is the patient responding to therapy or showing symptoms of toxicity?
2. Was the sample taken at steady state?
3. Was the sampling time appropriate for the drug?
4. Where is the concentration relative to the 'target' range (Table 1.3)?
5. If the patient is not responding or has toxicity, how should the dose be modified?

Unexpectedly low concentrations may indicate poor adherence or an absorption problem (e.g. secondary to vomiting).

Clearance estimates

The clinical significance of clearance is that it determines an individual patient's maintenance dose requirements. Clearance varies between individuals and within an individual in response to changes in his or her clinical condition.

The physiological and pathological factors that affect the clearance of a drug depend mainly on

Table 1.3 Examples of target ranges.

	Target range	
Drug	**Mass units**	**Molar units**
Digoxin	0.8–2 µg/L	1–2.6 nmol/L
Carbamazepine	4–12 mg/L	20–50 µmol/L
Phenytoin	10–20 mg/L	40–80 µmol/L
Gentamicin	5–12 mg/L (1 hour post-dose)	
Vancomycin	5–10 mg/L (trough)	
Theophylline	5–20 mg/L	28–110 µmol/L

In some hospitals, high aminoglycoside doses (e.g. gentamicin doses of 5–7 mg/kg) are given at intervals of 24–48 hours and the normal target peak and trough ranges do not apply. Samples are usually taken 6–14 hours after the dose and the dose is adjusted (if necessary) according to a nomogram.

which organ is primarily responsible for its elimination. For example, clearance of the bronchodilator theophylline, a drug that is eliminated by hepatic metabolism, is influenced by age, weight, alcohol consumption, cigarette smoking, other drugs, congestive cardiac failure, hepatic cirrhosis, acute pulmonary oedema and severe chronic obstructive airways disease.

Clearance in any individual is most accurately determined from concentration measurements. However, in many cases, relationships between clearance and clinical factors have previously been established. For example, the average value for theophylline clearance is 0.04 L/h/kg and this is modified according to the patient's clinical characteristics by multiplying by the factors shown in Table 1.4. This means that on average, smokers require 1.6 times the theophylline dose of non-smokers and patients with cirrhosis require half the dose of patients without cirrhosis.

Table 1.4 Factors influencing theophylline clearance and therefore dose requirements.

Factor	Adjustments required
Smoking	×1.6
Congestive cardiac failure	×0.4
Hepatic cirrhosis	×0.5
Acute pulmonary oedema	×0.5
Severe chronic obstructive airways disease	×0.8

For drugs primarily excreted by the kidney, e.g. digoxin and gentamicin, creatinine clearance closely reflects drug clearance. Thus, digoxin clearance can be estimated from the equation:

$$\text{Digoxin clearance} = \text{Creatinine clearance} + 0.33\,(\text{mL/min/kg}) \quad \text{(Eqn 1.1)}$$

The 0.33 in this equation represents the elimination by routes other than the kidney, such as metabolism and clearance by the hepatobiliary system.

An estimate of clearance can then be used to calculate the required dose to achieve a target concentration

$$\text{Maintenance dose rate} = \text{Clearance} \times \text{Target } Css_{\text{average}} \quad \text{(Eqn 1.2)}$$

$$\text{Maintenance dose} = \text{Clearance} \times \text{Target } Css_{\text{average}} \times \text{Dosage interval}/F \quad \text{(Eqn 1.3)}$$

where F represents oral bioavailability. Factors that influence clearance are now routinely investigated for all new drugs so that dosage adjustments can be made for patients with a low clearance, who might be at risk from toxicity.

Interpretation of serum concentrations

Serum concentrations can be measured for a number of reasons and it is important to interpret the measured concentration in the light of the clinical situation. If the aim is to assess the patient's maintenance dose requirements, samples should ideally be taken at steady state. However, confirmation of steady state is not necessary if the aim is to confirm toxicity and adherence or to assess the need for a loading dose in a patient who is acutely unwell.

Steady state normally requires that four to five half-lives elapse since treatment started or since any change in dose. Doses should be given at regular intervals and it is important to confirm that no doses have been omitted. If these conditions can be satisfied and the pharmacokinetics of the drug are linear,

clearance depends on the ratio of the dosing rate to the average steady-state concentration as can be seen by rearranging Eqn 1.2:

$$\text{Clearance} = \frac{\text{Maintenance dose rate}}{C\text{ss}_{\text{average}}} \qquad \text{(Eqn 1.4)}$$

This means that doses can be adjusted by simple proportion, i.e.

$$\text{Maintenance dose} = \left(\frac{\text{Desired } C\text{ss}_{\text{average}}}{\text{Measured } C\text{ss}_{\text{average}}}\right) \times \text{Current dose} \qquad \text{(Eqn 1.5)}$$

Concentrations that are not at steady state cannot be used in this way; although if accurate details of dosage history and sampling time are available, clearance may be estimated with the help of a pharmacokinetic computer package.

It is important to remember that drugs with non-linear kinetics (such as phenytoin) require special consideration, and different techniques are applied to the interpretation of their concentrations. Successful interpretation of a concentration measurement depends on accurate information. The minimum usually required is:

1. Time of sample collection with respect to the previous dose. Samples taken at inappropriate times may be misinterpreted. Usually, the simplest approach is to measure a trough concentration (i.e. at the end of the dosage interval)
2. An accurate and detailed dosage history – drug dose, times of administration and route(s) of administration. This information can be used to assess whether the sample represents steady state. Samples taken without knowledge of dosage history can result in an inappropriate clinical action or dosage adjustment
3. Patient details such as age, sex, weight, serum creatinine (and estimated glomerular filtration rate) and assessments of cardiac and hepatic function. This information helps to determine expected dose requirements and is necessary for all computerised interpretation methods. Knowledge about the stability of the patient can help to determine the frequency of monitoring, especially if the drug is cleared by the kidneys and renal function is changing
4. Changes in other drug therapy that might influence the pharmacokinetics of the drug being measured
5. The reason for requesting a drug analysis should be considered carefully. 'On admission' or 'routine' requests are usually of little value and are a waste of valuable resources

Clinical examples of therapeutic drug monitoring

Digoxin

Clinical scenario

Mr A.R., a 78-year-old man weighing 72 kg and with a creatinine clearance of 24 mL/min, has been taking 250 μg digoxin daily to control atrial fibrillation. He presents to his general practitioner with anorexia and nausea a month after starting therapy. A digoxin concentration of 3.6 μg/L (4.6 nmol/L) is measured.

Is this concentration expected?

His expected digoxin clearance can be calculated from Eqn 1.1, i.e.

$$\begin{aligned}\text{Digoxin clearance} &= \frac{24}{72} + 0.33\,(\text{mL/min/kg}) \\ &= 0.663\,\text{mL/min/kg} \\ &= 2.9\,\text{L/h}\end{aligned}$$

His average steady-state concentration can be estimated from Eqn 1.2, i.e.

$$\begin{aligned}\text{Predicted } C\text{ss}_{\text{average}} &= \frac{0.6 \times 250\,\mu\text{g}}{2.9 \times 24\,\text{h}} \\ &= 2.2\,\mu\text{g/L}\,(2.8\,\text{nmol/L})\end{aligned}$$

The 0.6 is an estimate of the bioavailability of digoxin tablets. The reason the measured concentration is higher than expected should be investigated. In this case, it was found that the sample had been withdrawn 2.5 hours after the dose. Digoxin is absorbed quickly but distributes slowly to the tissues. Samples taken before distribution is complete (i.e. less than 6 hours after the dose) and cannot be interpreted. As concentrations fall only by about 20% from 6 to 24 hours after the dose, samples can be taken at any time during this period.

A further (trough) sample withdrawn 24 hours after the last dose measured 2.4 µg/L (3.1 nmol L). This result is more consistent with the expected concentration but suggests that the dose is too high and may be contributing to his symptoms.

What dose adjustment should be made?

Digoxin has linear pharmacokinetics; therefore, the new dose can be determined by simple proportion. Table 1.5 shows that there are three dosage options for Mr A.R. A reduction to 125 µg/day is the most obvious first choice, but further adjustment (up or down) could be made if necessary on clinical grounds (e.g. poor control of atrial fibrillation or persistence of adverse effects).

Comment. This case illustrates the importance of sampling time for the correct interpretation of digoxin concentrations. Although digoxin is traditionally prescribed to be taken in the morning, changing to a night-time dose can reduce the chances of samples being withdrawn during the distribution phase. Digoxin has a long elimination half-life (50–100 hours) and elimination is slow beyond 6 hours after the dose. If samples are taken at steady state, dosage adjustment can be performed by simple proportion.

Gentamicin

Clinical scenario

Mr J.L., a 64-year-old man who weighs 80 kg and has an estimated creatinine clearance of 35 mL/min, requires gentamicin therapy for a suspected Gram-negative infection. The aim is to achieve a peak concentration around 8 mg/L and a trough around 1 mg/L.

Table 1.5 Predicted steady-state digoxin concentrations for clinical scenario.

Dose (µg)	$Css_{average}$ (µg/L)	Css_{trough} (µg/L)
250	3.0	2.4
187.5	2.2	1.8
125	1.5	1.2
62.5	0.75	0.6

What dosage regimen should be prescribed?

Gentamicin is cleared by excretion through the kidneys and its clearance can be approximated by creatinine clearance. The volume of distribution of gentamicin is around 0.25 L/kg. A dosage interval of about three half-lives will allow the concentration to fall from 8 to 1 mg/L (8 → 4 → 2 → 1). The elimination half-life can be calculated from Eqn 1.3, i.e.

$$t_{1/2} = \frac{\ln 2}{k}$$

$$t_{1/2} = \frac{0.693 \times V}{\mathrm{CL}}$$

$$t_{1/2} = \frac{0.693 \times 0.25\,\mathrm{l/kg} \times 80\,\mathrm{kg}}{35\,\mathrm{mL/min} \times (60/1000)}$$

$$= \frac{0.693 \times 20}{2.1\,\mathrm{L/h}}$$

$$= 6.6\,\mathrm{h}$$

It will therefore take 3 × 6.6 = 20 hours for the concentration to fall from 8 to 1 mg/L. Because the 'peak' is measured 1 hour after the dose, the dosage interval should be 21 hours. A 'practical' dosage interval is therefore 24 hours. The dose administered should increase the concentration by 7 mg/L (i.e. from 1 to 8 mg/L). It can be calculated from the volume of distribution, i.e.

$$\mathrm{Dose\,(mg)} = 7\,\mathrm{mg/L} \times 0.25\,\mathrm{L/kg} \times 80\,\mathrm{kg} = 140\,\mathrm{mg}$$

Mr J.L. was started on a daily dose of 140 mg and after 2 days of therapy his peak concentration (1 hour post-dose) was 6 mg/L and his trough (24 hours post-dose) was 0.5 mg/L.

Has steady state been reached?

Mr J.L.'s estimated elimination half-life is 6.6 hours; therefore, steady state should be reached in 5 × 6.6 = 33 hours. He will be at steady state after 2 days of therapy.

How should the dose be adjusted?

The peak is slightly lower than the target and the trough is satisfactory. As these represent steady-state concentrations and gentamicin has linear pharmacokinetics, the dose can be adjusted by proportion. Increasing the dose to 200 mg/day should achieve a peak of (200/140) × 6 = 8.6 mg/L and a trough of (200/140) × 0.5 = 0.7 mg/L.

Comment. Elimination half-life is a useful guide to dosage interval and is particularly important when

the target concentration–time profile includes both peak and trough concentrations. In this case, because the peaks and troughs were both low, the dose can be adjusted by direct proportion. If the trough had been high, an increase in the dosage interval would also have been necessary.

Phenytoin

Clinical scenario

Mrs D.L., a 38-year-old woman who weighs 55 kg, was prescribed phenytoin at a dose of 300 mg/day (5.5 mg/kg/day) after carbamazepine failed to control her epilepsy. She attended the outpatient clinic 3 weeks later and her 24-hour post-dose trough phenytoin concentration was 6 mg/L (24 μmol/L). As her seizures were not well controlled, her dose was increased to 350 mg/day (6.4 mg/kg/day). She presented to her general practitioner 2 weeks later complaining of fatigue and difficulty in walking properly. Her trough phenytoin concentration was 28 mg/L (112 mol/L).

Why was the first concentration so low?

There are two possibilities: the dose was too low, or she was not adhering to her prescribed dose. As patients generally require phenytoin maintenance doses in the range 4.5–5 mg/kg/day, both doses were higher than average. Phenytoin has non-linear pharmacokinetics at concentrations normally seen clinically, and standard pharmacokinetic equations cannot be used. The relationship between dose rate and average steady-state concentration is controlled by V_{max} (the maximum amount of drug that can be metabolised by the enzymes per day) and K_m (the concentration at half V_{max}). Using average values of V_{max} (7.2 mg/kg/day) and K_m (4.4 mg/L), Mrs D.L.'s expected concentration can be calculated from the Michaelis–Menten equation:

$$\text{Dose rate} = \frac{V_{max} \times Css}{K_m + Css}$$

$$Css = \frac{\text{Dose rate} \times K_m}{V_{max} - \text{Dose rate}}$$

$$Css = \frac{300\,\text{mg/day} \times 4.4\,\text{mg/L}}{(7.2 \times 55)\,\text{mg/day} - 300\,\text{mg/day}}$$

$$= \frac{1320}{96}$$

$$= 14\,\text{mg/L}\,(55\,\mu\text{mol/L})$$

The measured concentration of 6 mg/L is much lower than expected and suggests poor adherence with therapy.

Why was the second concentration so high?

The predicted concentration on her increased dose can be calculated as before, i.e.

$$Css = \frac{350\,\text{mg/day} \times 4.4\,\text{mg/L}}{(7.2 \times 55)\,\text{mg/day} - 350\,\text{mg/day}}$$

$$= \frac{1540}{46}$$

$$= 33\,\text{mg/L}\,(147\,\mu\text{mol/L})$$

In this case, the measured concentration was reasonably consistent with the predicted value and her actual V_{max} can therefore be estimated from the measured concentration, i.e.

$$V_{max}\,(\text{mg/day}) = \frac{\text{Dose rate} \times (K_m + Css)}{Css}$$

$$V_{max}\,(\text{mg/day}) = \frac{350\,\text{mg/day} \times (4.4 + 28)\,\text{mg/L}}{28\,\text{mg/L}}$$

$$= 450\,\text{mg/day}$$

Using her actual V_{max} and a K_m of 4.4 mg/L, average steady-state concentrations can be predicted for various doses (Table 1.6). Note that a small change in the dose produces a disproportionately large increase in concentration, especially at higher concentrations.

Table 1.6 Predicted steady-state phenytoin concentrations for clinical scenario.

Dose (mg/day)	Steady-state concentration (mg/L)	(μmol/L)
225	6	24
250	7	28
275	9	36
300	13	52
325	18	72
350	28	112
375	55	220

It is known that a concentration of 6 mg/L does not control her seizures and she experiences toxicity with 28 mg/L. Her ideal dose is therefore likely to lie in the range 275–325 mg/day. It would be sensible to start with 300 mg/day and adjust the dose (if necessary) according to her response. It would also be useful to emphasise to the patient that she must comply with her prescribed dose in order to obtain the maximum benefit from her therapy.

Comment. This case illustrates the non-linearity of phenytoin dose–concentration relationships and the difficulty of interpreting phenytoin concentrations when dosage history is uncertain (as frequently occurs with outpatients). It also demonstrates the value of using serial measurements (the two results were clearly inconsistent with each other) and average dose requirements to assess adherence.

Influence of renal function on pharmacokinetics and pharmacodynamics

Drugs are usually considered in terms of their effect on disease processes. However, several diseases can influence the pharmacokinetics of a drug or its pharmacological effect on target organs. Diseases of the liver and kidney are of particular importance due to the role of these organs in elimination of drugs. This chapter will discuss the important considerations which arise when prescribing for a patient with these co-morbidities.

Clinical scenario

A 45-year-old woman is admitted to hospital with severe urosepsis. She gives a background history of recurrent urinary infections and chronic renal impairment secondary to structural abnormalities of the urinary tract. Blood and urine culture reveals growth of Gram-negative bacilli sensitive to gentamicin. How may this patient's renal function influence the treatment of her presenting complaint, and what precautions should be considered?

Influence of impaired renal function

KEY POINTS

Impaired renal function can influence drug therapy for the following reasons:

1. **Pharmacokinetics may be altered as result of:**
   - **Decreased elimination of drugs that are normally excreted entirely or mainly by the kidneys**
   - **Decreased protein binding**
   - **Decreased hepatic metabolism**
2. **Drug effect may be the altered**
3. **Existing clinical condition may be worsened**
4. **Adverse effects may be enhanced**

Altered pharmacokinetics

Elimination

Because the kidney represents one of the major routes of drug elimination, a decline in renal function can influence the clearance of many drugs. If a drug normally cleared by the kidney is given to someone with decreased renal function without altering the dose, the steady-state blood concentrations of that drug will be increased. This is of considerable importance in the case of drugs showing concentration-related effects, particularly those that have a narrow therapeutic range.

When such drugs are given to patients with renal dysfunction, the general aim is to achieve similar concentrations to those seen in patients with normal kidneys.

Therapeutic concentrations can be maintained by:

1 Determining renal function, usually by estimating creatinine clearance

2 Modifying the dose using a nomogram, either by increasing the dosage interval, or by giving a lower dose at the same interval or by altering both the dose and the interval. The extent and precision of dose modification depend very much on the toxicity of the drug concerned. In the case of the aminoglycosides, even minor impairment of renal function requires some dosage alteration, while the dose of penicillins need only be reduced in severe renal failure (creatinine clearance <10 mL/min). Guidance on dosage modification is readily available for most commonly used drugs. It should

be noted that the loading dose is usually not changed by renal impairment because this depends more on the volume of distribution of the drug than its rate of elimination

3 Monitoring drug concentrations. This is useful for drugs with concentration-related adverse effects, such as the aminoglycosides, digoxin, aminophylline, phenytoin and carbamazepine, and mandatory for lithium, ciclosporin (cyclosporin) and methotrexate. Nomograms are useful guides to the doses likely to be appropriate, but every patient is different. Concentrations of drugs in the blood can be used to assess clearance and to determine the most appropriate dose for individual patients

Decreased protein binding

The following changes occur in patients with impaired renal function:

1 Acidic drugs are less bound to serum albumin and the decrease in binding correlates with the severity of renal impairment. The binding of basic drugs (to α_1-acid glycoprotein) undergoes little or no change
2 The structure of albumin is changed in renal failure and endogenous compounds may compete with drugs for binding
3 Haemodialysis does not return binding to normal, but renal transplantation does.

In most cases, changes in protein binding have limited clinical relevance and do not require alterations in dose. However, protein binding is important for the interpretation of serum phenytoin concentrations.

Influence hepatic disease on pharmacokinetics and pharmacodynamics

Hepatic metabolism

The hepatic metabolism of some drugs (e.g. nicardipine, propranolol) may be decreased in patients with renal failure. The reasons for this are not clear, but may indicate the presence of a metabolic inhibitor in uraemic plasma because regular haemodialysis appears to normalise the clearance of these compounds.

Altered drug effect

There are several examples of increased drug sensitivity in patients with renal failure. Opiates, barbiturates, phenothiazines and benzodiazepines all show greater effects on the nervous system in patients with renal failure than in those with normal renal function. The reasons are not known, but increased meningeal permeability is one possible explanation.

Various antihypertensive drugs have a greater postural effect in renal failure. Again the reasons are not clear, but changes in fluid balance and autonomic dysfunction may be partly responsible.

Worsening of the existing clinical condition

Drug therapy can result in deterioration of the clinical condition in the following ways:

1 By further impairing renal function. In patients with renal failure, it is clearly advisable to avoid drugs that are known to be nephrotoxic and for which alternatives are available. Examples include aminoglycosides, amphotericin, cisplatin, gold, mesalazine, non-steroidal anti-inflammatories, penicillamine and vancomycin
2 By causing fluid retention. Fluid balance is a major problem in the more severe forms of renal failure. Drugs that cause fluid retention should therefore be avoided, e.g. carbenoxolone and non-steroidal anti-inflammatory drugs (NSAIDs) such as indometacin (indomethacin)
3 By increasing the degree of uraemia. Tetracyclines, except doxycycline, have an anti-anabolic effect and should be avoided

Enhancement of adverse drug effects

In addition to decreased elimination, digoxin is more likely to cause adverse effects in patients with severe renal failure if there are substantial electrolyte abnormalities, particularly hypercalcaemia and/or hypokalaemia.

Because potassium elimination is impaired in renal failure, diuretics that also conserve potassium (amiloride, spironolactone) are more likely to cause hyperkalaemia.

Influence of liver disease

Impaired liver function can influence the response to treatment

1. Altered pharmacokinetics:
   - Increased bioavailability resulting from reduced first-pass metabolism or, potentially, decreased first-pass activation of pro-drugs
   - Decreased protein binding
2. Altered drug effect
3. Worsening of metabolic state

Altered pharmacokinetics

The liver is the largest organ in the body, has a substantial blood supply (around 1.5 L/min) and is interposed between the gastrointestinal tract and the systemic circulation. For these reasons it is uniquely suited for the purpose of influencing drug pharmacokinetics.

Decreased first-pass metabolism

A decrease in hepatocellular function decreases the capacity of the liver to perform metabolic processes, while portosystemic shunting directs drugs away from sites of metabolism. Both factors are usually present in patients with severe cirrhosis.

Knowledge of the drugs that undergo first-pass metabolism is important in situations where it is decreased as a result of disease. Considerably greater quantities of active drug then reach the site of action and any given dose of drug has unexpectedly intense effects.

Examples of changes in bioavailability found in some patients with severe cirrhosis are:

- Clomethiazole (chlormethiazole) (100% increase)
- Labetalol (91% increase)
- Metoprolol (65% increase)
- Nicardipine (500% increase)
- Paracetamol (50% increase)
- Propranolol (42% increase)
- Verapamil (140% increase)

Conversely, first-pass activation of pro-drugs such as many ACE inhibitors (e.g. enalapril, perindopril, quinapril) may potentially be slowed or reduced.

Decreased elimination by liver metabolism and decreased protein binding

High extraction drugs

These are drugs which the liver metabolises at a very high rate. Their bioavailability is low and their clearance is dependent mainly upon the rate of drug delivery to the enzyme systems. The clearance of these drugs is therefore relatively sensitive to factors that can influence hepatic blood flow, such as congestive cardiac failure, and relatively insensitive to small changes in enzyme activity or protein binding. Examples include labetalol, lidocaine, metoprolol, morphine, propranolol, pethidine, nortriptyline and verapamil.

Low extraction drugs

In low extraction drugs, the rate of metabolism is so sufficiently low that hepatic clearance is relatively insensitive to changes in hepatic blood flow, and dependent mainly on the capacity of the liver enzymes. Examples include chloramphenicol, paracetamol and theophylline. The hepatic clearance of drugs in this group that are also highly protein-bound, such as diazepam, tolbutamide, phenytoin and valproic acid, depends on both the capacity of the enzymes and the free fraction. It is thus difficult to predict the consequences of hepatic disease on total drug concentration. However, as with renal disease, care must be taken in the interpretation of concentrations of highly protein-bound drugs such as phenytoin.

The influence of liver disease on drug elimination is complex; the type of liver disease is critical. In acute viral hepatitis, the major change is in hepatocellular function, but drug-metabolising ability usually remains intact and hepatic blood flow can increase. Mild to moderate cirrhosis tends to result in decreased hepatic blood flow and portosystemic shunting, while severe cirrhosis usually shows reduction in both cellular function and blood flow. Cholestasis leads to impaired fat absorption with deficiencies of fat-soluble vitamins and impairment of absorption of lipophilic drugs. Alcoholic liver disease is common and chronic ethanol abuse is associated with increased activity of the microsomal ethanol-oxidising system. This effect is a result primarily of induction by ethanol of a specific cytochrome P450 (CYP2E1) responsible for enhanced oxidation of ethanol and other P450 substrates and, consequently, for metabolic tolerance to these substances. This may lead to enhanced clearance and, hence, decreased response to certain drugs such as benzodiazepine sedatives, anticonvulsants (phenytoin) and warfarin. By contrast, simultaneous alcohol ingestion may decrease clearance of drugs metabolised via the P450 (CYP2E1) enzyme system.

Comment. Unlike the measurement of creatinine clearance in renal disease, there is no simple test that can predict the extent to which drug metabolism is decreased in liver disease. A low serum albumin, raised bilirubin and prolonged prothrombin time give a rough guide.

The fact that a drug is metabolised by the liver does not necessarily mean that its pharmacokinetics is altered by liver disease. It is not easy, therefore,

to extrapolate the findings from one drug to another. This is because superficially similar metabolic pathways are mediated by different forms of cytochrome P450.

The documentation of modestly altered pharmacokinetics does not necessarily imply clinical importance. Even normal subjects show quite wide variations in pharmacokinetic indices and therefore pharmacokinetics should not be viewed in isolation from alterations in drug effect, which are much more difficult to assess. However, if a drug is known to be subject to substantial pharmacokinetic changes, clinical significance is much more likely.

If it is clinically desirable to give a drug that is eliminated by liver metabolism to a patient with cirrhosis, it should be started at a low dose and the drug levels or effect monitored very closely.

Altered drug effect deranged brain function

The more severe forms of liver disease are accompanied by poorly understood derangements of brain function that ultimately result in the syndrome of hepatic encephalopathy. However, even before encephalopathy develops, the brain is extremely sensitive to the effects of centrally acting drugs and a state of coma can result from administering normal doses of opiates or benzodiazepines to such patients.

Decreased clotting factors

Patients with liver disease show increased sensitivity to oral anticoagulants. These drugs exert their effect by decreasing the vitamin K-dependent synthesis of clotting factors II, VII, IX and X. When the production of these factors is already reduced by liver disease, a given dose of oral anticoagulant has a greater effect in these patients than in subjects with normal liver function.

Worsening of metabolic state

Drug-induced alkalosis

Excessive use of diuretics can precipitate encephalopathy. The mechanism involves hypokalaemic alkalosis, which results in conversion of NH_4^+ to NH_3, the un-ionised ammonia crossing easily into the central nervous system to worsen or precipitate encephalopathy.

Fluid overload

Patients with advanced liver disease often have oedema and ascites secondary to hypoalbuminaemia and portal hypertension. This problem can be worsened by drugs that cause fluid retention, e.g. NSAIDs, and antacids that contain large amounts of sodium. NSAIDs should be avoided anyway, because of the increased risk of gastrointestinal bleeding.

Hepatotoxic drugs

Where an acceptable alternative exists, it is wise to avoid drugs that can cause liver damage (Table 1.7), e.g. sulphonamides or rifampicin, and repeated exposure to halothane anaesthesia.

Table 1.7 Drugs that can cause liver damage.

Hepatitis
- Halothane (repeated exposure)
- Isoniazid
- Rifampicin
- Methyldopa
- Phenelzine
- Trimipramine
- Desipramine
- Carbimazepine
- Trasidone
- Propylthiouracil
- Augmentin
- Erythromycin
- Nitrofurantoin
- Chloroguanide
- Tienilic acid
- Dihydralazine
- Azothiaprine
- Sulfasalazine (sulphasalazine)
- Naproxen
- Amiodarone

Cholestasis with mild hepatic component
- Phenothiazines
- Carbamazepine
- Tricyclic antidepressants
- Non-steroidal anti-inflammatory drugs (especially phenylbutazone)
- Rifampicin, ethambutol, pyrazinamide
- Sulphonylureas, trimethoprim
- Sulphonamides, ampicillin, nitrofurantoin, erythromycin estolate
- Oral contraceptives (stasis without hepatitis)

Cirrhosis
- Methotrexate

Prescribing for the young and the elderly

Prescribing for the young

Clinical scenario

A 4-year-old girl presents with her mother to the emergency department with shortness of breath, wheeze and a temperature. Her past medical history includes premature birth at 34 weeks gestation and asthma. She is prescribed salbutamol inhaler as required at home, which she has been using more frequently in the last 2 days. On examination, she is breathless at rest, is pyrexial, tachycardic and has bilateral rhonchi. She weighs 15 kg. A diagnosis of moderate acute exacerbation of asthma is made. You are asked to prescribe an antipyretic medication, salbutamol and prednisolone.

Introduction

Prescribing in children (neonate to 16 years old) should always be undertaken with care. There are significant differences between children and adults in terms of pharmacokinetics, pharmacodynamics and practical aspects of drug treatment. Children should not be regarded simply as small adults as dosing requires calculation based on weight, age, surface area and renal function. Prescribing for children comes with significant risks of errors and potential harm and therefore should not be carried out if inexperienced without senior medical or specialist pharmacy support.

Pharmacokinetics

A variety of factors influence pharmacokinetics in the young. Drug absorption may be affected by relatively high gastric pH in infants, and topical preparations are better absorbed because the skin is relatively thin. Low body fat content may reduce the volume of distribution of lipophilic drugs, and lower plasma albumin concentration reduces plasma protein binding. Immaturity of neonatal hepatic enzyme systems and renal excretion mechanisms may impair drug elimination, necessitating dosage reduction in the first months of life.

Pharmacodynamics

The differential effects of some drugs in children compared with adults are well recognised, an example being the sedative effect of stimulant amphetamine derivatives in children, a paradoxical effect used in the management of ADHD. Although effects such as this are recognised, the mechanisms are poorly understood.

Practical aspects of prescribing in children

Medicine has no benefit if the child refuses to take prescribed substances due to unpleasant taste, bulky formulation or lack of understanding of the necessity to take the prescription. Many children's medicines contain excipients, aiming to make them more palatable. However, less used medicines may not. Discussion with parents regarding reward style encouragement or offering advice as to food/drinks which the medicine can be mixed with to improve the taste may help.

Physical and developmental stages should also be considered. For example, the management of common childhood complaints like asthma can be complicated by the need to acquire an effective inhaler technique, which younger children find difficult.

For children, social aspects of taking medicine are also important. Being 'different' from classmates or friends may impact on adherence to medication, particularly prevalent in children with diabetes requiring insulin. Taking time to explore the child's concerns may prevent potentially life-threatening complications.

Safety

Safety is paramount when prescribing for children as overdosing and adverse effects can be serious. Abbreviations such as mcg, mg, ng and mL should be avoided and the full instruction written (e.g. micrograms, nanograms or milligrams). This helps to avoid errors, as doses are as likely to be ng as they are mg depending on the weight of the child and can be easily misread. One vial of drug may contain enough active product to overdose a child by 10 or 100 fold. For example, a vial of morphine sulphate contains 10 mg (10 mL) of substance. In a neonate, the recommended dose is 5–20 µg/kg/h, which in a normal 3 kg baby would only equate to a 15–60 µg (0.15–0.6 mL) dose. Therefore, one vial contains enough solution to significantly overdose the child.