Hepler and Segel (2003) calculated that the effects of prescribed drug therapy are currently the fourth leading cause of all deaths in the US and, by extension, in other developed countries as well.

Practitioners involved in deciding dose levels for drugs need to be aware of the rate at which drugs are absorbed by the body and distributed to the point of action, as well as the rate at which they are excreted from the body or broken down (metabolised) while in the body.

On successful completion of this topic you will:
• understand the pharmacokinetic and pharmacodynamic behaviour of drugs (LO2).

To achieve a Pass in this unit you need to show that you can:
• discuss the influence of route of administration on systemic toxicity (2.1)
• review pathways of drug metabolism (2.2)
• explain methods of biological evaluation of drugs (2.3)
• explain abnormal responses to drugs (2.4).
The influence of route

Methods of administration

The majority of drugs reach their site of action via the bloodstream and several factors need to be taken into account to be able to predict the final plasma concentration of the drug in the bloodstream from the administered dose. Higher blood plasma concentrations mean a higher chance of side effects or exceeding the toxic threshold.

A smaller number of drugs are applied directly to their point of action – for example, eye drops to treat glaucoma, steroid creams for dermatitis and even the bronchodilators that treat asthma. These drugs are described as topical and act locally – hence the chances of side effects are greatly diminished.

Pharmacokinetics and drug administration

Drugs can be administered by a variety of routes, the most common and convenient being via an oral route by swallowing pills or suspensions of the drug. Other enteral routes include the use of suppositories or enemas, where the drug is introduced through the rectum.

Examples of parenteral methods of administration include intravenous or intramuscular injection, as well as drugs that dissolve under the tongue and those that are absorbed through the skin before entering the gastrointestinal system.

Absorption

Except for the topical drugs discussed above, most drugs need to be absorbed into the bloodstream to be able to reach their target. This will usually require the drug to cross cell membranes (for example, from the intestine into the cells that line the intestine).

Many fat-soluble drugs can diffuse through the cell membrane down a concentration gradient; only a small number of drugs (such as the anticancer drug, fluorouracil) are absorbed by an active transport mechanism.

Drug case study

Glyceryl trinitrate (GTN) is used to treat angina. It can be administered as a mouth spray and is absorbed very quickly as it is a low molecular mass molecule.

- Why is it important that absorption happens as quickly as possible in angina treatment?

If a very rapid effect is needed, a drug can be injected intravenously so there is no need for the drug to cross cell membranes.

Drug case study

Diazepam can be used to treat potentially harmful seizures, such as those in an epileptic seizure. In this emergency situation, an intravenous injection would provide the fastest absorption route but is not really practical during a seizure. However, as the drug is very lipid soluble, rectal administration is also very rapid and this is often the preferred route.

- What possible reasons can you give for not attempting to give the drug orally in this case?
Distribution

This is the dispersion of the drug around the body in the bloodstream. The rate at which it reaches a particular tissue will depend only on the rate of blood supply to that tissue.

The brain, heart and lungs are well supplied with blood and the concentration of a drug in these tissues rises rapidly over a period of a few minutes following absorption into the bloodstream. In tissues such as muscle or joints, the drug concentration may not reach maximum until an hour or so after absorption; after reaching peak concentration, the graphs for both plasma and tissue concentration decay away, because the drug may then be metabolised and excreted (see Figure 9.2.1).

Many drugs are actually transported around the bloodstream bound to plasma proteins, which makes them inactive. This does not cause a problem as the bound drug is in equilibrium with the free drug and hence the drug molecule is released when the concentration of the free drug falls. Problems can arise if other drugs compete for the binding site on the plasma protein and, for a small number of drugs, this is a significant issue.

Drug case study

Warfarin is used as an anticoagulant to prevent the occurrence of blood clots in blood vessels. Almost all the warfarin in the bloodstream is bound to plasma proteins. Other drugs, such as the antibiotics ciprofloxacin and erythromycin, bind to the same plasma protein so, if these drugs are taken by a patient on warfarin, problems could be caused. The antibiotics displace the warfarin, causing a rapid rise in free warfarin and resulting in uncontrolled bleeding.

- About 97% of warfarin in the bloodstream is usually bound to plasma proteins. The presence of an antibiotic might cause this to fall to 94%. Explain why this small change causes a very large biological effect on the clotting behaviour of the blood.

Metabolism

The human body is generally very effective at getting rid of potentially toxic substances present in the bloodstream – which, of course, includes drugs. This detoxification process involves deactivating the drug and then excreting the water-soluble metabolites via the kidneys.
The process of inactivation of drugs occurs largely (but not exclusively) in the liver and involves enzymatic processes that alter the chemical structure of the drug (for example, by adding hydroxyl groups or removing alkyl groups). These processes make the drug less fat soluble and more water soluble, preventing its absorption into tissue, and can be inhibited or enhanced by the presence of other drugs or their metabolites with very significant implications for the prescriber of drugs.

Excretion

As noted above, inactivation of a drug often involves reducing its fat solubility. This also has the effect of increasing its water solubility and hence allows it to be excreted via the kidneys. In some cases the inactivation process, often known as phase 1 metabolism, has to be followed by a second process (phase 2) in order to create a sufficiently water-soluble product.

A simple example of this is aspirin (acetylsalicylic acid), seen in Figure 9.2.2, which is hydrolysed into salicylic acid in a phase 1 process and then made more water soluble by the attachment of a highly polar glucuronide group in a phase 2 reaction.

![Figure 9.2.2: Aspirin is metabolised by the liver into the water-soluble compound, salicylic glucuronide. From left to right these symbols show aspirin, salicylic acid and salicylic glucuronide.](image)

The kidneys excrete these water-soluble products into the urine. However, other routes significant for some drugs include excretion into breast milk and from the liver into the intestine via the bile duct. These alternative routes have implications for the prescribing of those drugs.

Drug case study

Practitioners giving advice to women taking the contraceptive pill will need to be aware of bile excretion processes. The oestrogen in the oral contraceptive pill is metabolised in the liver by combination with glucuronide to form a water-soluble conjugate that is excreted directly into the intestine. Enzymes in the intestine break this down into free oestrogen, which is reabsorbed through the intestinal wall. This means that oestrogen levels in the body can remain at a level high enough to prevent ovulation even though the dose in each contraceptive pill is quite low. However, practitioners must make women aware that bouts of diarrhoea can cause the oestrogen level to drop below this level; diarrhoea causes the rate of flow of fluids in the intestine to increase, which means that there may be insufficient time for reabsorption to occur.

- What advice should be given to a woman who is taking the contraceptive pill but who has just suffered a bout of diarrhoea?

Pharmacokinetics and systemic toxicity

The key issue for any drug prescriber is to ensure that the mean plasma concentration (and hence the tissue concentration) of the drug is maintained at a level high enough for the drug to work effectively over the required period, without ever reaching a level where it may display toxic effects.

Toxic effects occur because drugs designed to interact with receptors in particular tissues or systems will also interact with those receptors in other parts of the body.
Drug toxicity and dose regimen

When a practitioner is designing a dosing regimen the aim will be to ensure that the concentration of a drug reaches a steady state – that is, when the rate at which the drug is absorbed into the bloodstream is equal to the rate at which it is metabolised and excreted.

Plasma concentrations decay in an exponential way, and hence the half-life ($t_{\frac{1}{2}}$) can be calculated.

Activity

(Pass level) Look at the graph in Figure 9.2.3 showing how the plasma concentration of a drug decays over time. Use the graph to estimate the half-life of this drug in blood plasma.

Unless the drug is being given continuously, for example, via a drip, the patient will be receiving doses at regular intervals. If the half-life of the drug is relatively long (a few hours or more), the aim of the dosage regimen will be to achieve a situation in which the plasma concentration oscillates within the therapeutic range (see Figure 9.2.3). The exact dose required to maintain this level will also depend on patient-specific factors such as body weight, age and sex.

Drug case study

Paracetamol, a familiar analgesic (painkiller) is available over the counter. It has a half-life of 4 hours and a therapeutic range of 5–20 mg per litre. However, if high plasma concentrations of 150–200 mg per litre are reached, due to accidental or deliberate overdosing, then potentially fatal liver damage can occur. Doctors treating overdose patients can measure the current plasma concentration, and, if the approximate time of overdose is known, they can use the concept of half-life to calculate the likely peak concentration. If this exceeds the toxicity threshold then immediate treatment must be given.

Checklist

At the end of this section you should be familiar with the following ideas:
- the concentration of a drug in plasma or tissue depends on the processes of absorption, distribution, metabolism and excretion
- the route of administration affects the rate of absorption (and sometimes of metabolism)
- dosing regimens are designed to achieve a steady state of drug concentration.
Drug metabolism

As you saw in the previous section, most drugs will be gradually metabolised by the liver. In most cases this will inactivate the drug and allow the drug (or its metabolites) to be excreted. In some cases, drugs are actually activated by this process, and it is the metabolite that has pharmacological activity (see the case study about enalaprilat below).

Drug case study

Enalaprilat acts as an inhibitor of the angiotension-converting enzyme that causes restriction of blood vessels and hence can be used to treat hypertension (high blood pressure).

However, with two carboxylic acid groups, this molecule was too ionic to be able to be absorbed across the cell membrane of the gastrointestinal tract and would need to be administered intravenously rather than orally, which is clearly inconvenient.

The solution was to modify the drug by esterifying one of the carboxylic acid groups to form the molecule enalapril. In the liver, the ester group is hydrolysed back to the carboxylic acid group and the molecule becomes active.

Sites of metabolism

The smooth endoplasmic reticulum of liver cells is the primary site of drug metabolism. However, many of the enzymes responsible for metabolism are found in the cells of other tissues and metabolism can occur, for example, in the walls of the gastrointestinal tract, lungs, skin and kidney.

Pathways of metabolism

In section 1 it was mentioned that metabolic pathways are classified as phase 1 or phase 2 and involve modifying the drug to make it less fat soluble and more water soluble. This reduces the ability of the drug to cross cell membranes and increases excretion rates.

The chemical processes involved in phase 1 metabolism are generally modifications of a functional group – for example oxidation, hydroxylation (addition of an OH group) or the removal of an alkyl group. These occur via the action of a group of enzyme structures known as the cytochrome P450 oxidase system (often referred to as CYP isoenzymes).

In phase 2, the metabolite becomes chemically bonded (‘conjugated’) to an additional chemical group, such as the highly polar glucuronide group.

Activity

Explain why the glucuronide group (derived from glucuronic acid, shown in Figure 9.2.5) makes a drug molecule more polar.
Drug case study
Diazepam is a sedative used in treatment of anxiety and insomnia. It is metabolised by two different pathways to produce hydroxylated metabolites, oxazepam and temezepam. These are then conjugated with a glucuronide group in phase 2 reactions before being excreted.

Oxazepam and the two intermediates, nordazepam and temazepam are also prescribed as sedatives for a variety of conditions.

Figure 9.2.6: The phase 1 metabolism of diazepam.

1 Metabolism of the intermediate compound nordazepam is often observed to be slowed down in some elderly patients. Why would this be particularly significant when designing a dosing regimen for diazepam?
2 Use the structures of the molecules in Figure 9.2.6 to explain why temazepam and oxazepam can be conjugated with a glucuronide group but not diazepam or nordazepam.

Factors affecting rate of drug metabolism
Dose
Clearly the rate at which a drug is metabolised, and hence the rate at which metabolites may build up prior to excretion, depends on the initial dose. The metabolism of a drug is usually a first-order reaction (which is why the half-life of the drug is generally constant in any given individual), and this means that if the plasma concentration is doubled, the rate will also double.

Route of administration
In some cases, however, the rate of metabolism may be greater than expected for a given plasma concentration. This only occurs for drugs that are administered orally. They enter the bloodstream via the gastrointestinal system and pass through the liver before being distributed more widely; if the drug is efficiently metabolised by the liver then the concentration of the drug may be significantly reduced. This effect does not occur with other routes of administration such as intravenous injection.
In the workplace

Prescribing for the elderly brings with it great challenges for the GP or hospital clinician. It is estimated that around a third of all prescriptions are for patients of 65 or over, and over a quarter of all adverse drug reactions are observed in this age group. The reasons are not difficult to deduce – older patients will generally display reduced drug metabolism and reduced excretion rate. Half-lives may double or even quadruple (in the case of diazepam).

Elderly patients are also more likely to be on multiple medications. The chances of adverse drug interactions will grow exponentially as the number of drugs taken concurrently rises, so careful cross-checking of the British National Formulary (BNF) is vital.

Patient-specific factors

Age, sex and body weight, as well as general health and lifestyle, will all affect the rate of metabolism. Standard doses may therefore not be appropriate to every patient. In addition, there are a number of genetic factors that can cause very specific effects on drug metabolism, due to altered versions of one or more CYP enzymes. Individuals with these altered enzymes may display rates of metabolism of a particular drug between 10 and 100 times slower than usual.

Take it further

To find out more about the issues surrounding the prescription of drugs for the elderly, The Merck Manual, available online at [www.merckmanuals.com/professional/geriatrics/drug_therapy_in_the_elderly/drug-related_problems_in_the_elderly.html](http://www.merckmanuals.com/professional/geriatrics/drug_therapy_in_the_elderly/drug-related_problems_in_the_elderly.html), provides detailed information.

Case study

About 8% of Caucasians have been found to display very slow metabolism of certain antidepressants, antiarrhythmic agents, beta blockers and opiates. As a result, several potentially serious adverse drug reactions can occur in these individuals. They possess two abnormal alleles of a gene for the enzyme CYP2D6. Because of the relatively high percentage of this population displaying slow metabolism, practitioners need to be aware of the drugs metabolised by CYP2D6 and to carefully monitor any patient for whom they prescribe these drugs.

- Some drugs, such as beta blockers, are converted by CYP2D6 into compounds with a stronger effect than the original drug. What implications does this have for an individual with slow CYP2D6 metabolism who is taking beta blockers?

Drug interactions

As the range of drug treatments available to prescribers increases, the consideration of possible adverse drug interactions (ADIs) becomes ever more complex. Computer databases have greatly simplified the process, but an understanding of the ways in which interaction between drugs can occur is still critical for the practitioner. The interactions are difficult to predict because the drugs concerned often have completely different physiological effects and modes of action.

ADIs may involve drugs that are usually taken as self-medication, such as antacids, or even substances not usually categorised as drugs, for example, the furanocoumarin derivatives found in grapefruit juice.
In the workplace

The British National Formulary (BNF) is the standard reference work used by prescribers. It is published jointly by the British Medical Association and the Royal Pharmaceutical Society and includes key information on the selection, prescribing, dispensing and administration of medicines. Practitioners can use either a printed or online version; adverse drug interactions are dealt with in Appendix 1.

You can find out more and even register to use the site at http://www.bnf.org/bnf/index.htm.

Mechanisms of adverse drug interactions

ADIs can occur at many of the phases of drug activity – absorption, distribution, metabolism, excretion and the actual binding to receptor sites; it is this variety of mechanism that makes the interaction of drugs so difficult to predict. Examples of some of these, for example, the ability of some antibiotics to compete for plasma proteins in the distribution phase, have already been mentioned.

One of the most common ways in which drug interactions occur is when one drug inhibits a CYP enzyme necessary for the metabolism of a second, leading to a rise in plasma concentration of this second drug.

Drug case study

Antacids commonly contain metal ions such as aluminium, magnesium or calcium. These ions can form stable complexes with several drugs, including common antibiotics such as tetracycline and ciprofloxacin. The large, electrically charged complex is insufficiently lipid soluble to be absorbed from the gastrointestinal tract.

1. If a patient taking a course of tetracycline then starts taking antacids, what is likely to happen to the plasma concentration of the antibiotic?
2. What implications might this have for the patient?

Drug case study

Cimetidine is available as an over-the-counter treatment for heartburn and peptic ulcers. However it inhibits a wide range of enzymes in the cytochrome P450 system (CYP enzymes) and hence slows down the metabolism of many widely-used drugs, such as the antibiotic erythromycin, the anti-malarial chloroquine and beta blockers such as labetalol. Both the prescribers and pharmacists needs to be well aware of the range of interactions.

1. If a patient taking a course of erythromycin then starts taking cimetidine, what is likely to happen to the plasma concentration of the antibiotic?
2. What implications might this have for the patient?

Portfolio activity (2.1, 2.2)

Write a report explaining the potential dangers of systemic toxicity of paracetamol (also known as acetaminophen), or another drug of your choice.

In your report you should:
- describe the way in which paracetamol (or your chosen drug) is administered and the implications for the rate of absorption
- comment on the distribution of paracetamol (or your chosen drug) to tissues relevant to its mode of action
- explain how paracetamol (or your chosen drug) is metabolised and hence excreted
- describe the potential risks of toxicity if the safe dose is exceeded.

Activity

Research two different adverse drug interactions. Find out which phase of drug activity is involved in the interaction and write a short description of how the adverse drug interaction occurs, using ideas that you have encountered in this course.

Checklist

At the end of this section you should be familiar with the following ideas:
- metabolism of drugs takes place largely in the liver and renders drugs inactive and able to be excreted
- metabolic pathways involve making drugs less fat soluble and more water soluble
- the method of administration, presence of other drugs and factors specific to the patient all affect metabolic processes.
Bringing a new pharmaceutical product from design or discovery to market must surely be among the longest and most expensive procedures of any commercial product.

### Timeline for biological evaluation

You can watch a video describing the sequence of processes that occur to evaluate the safety and efficacy of a drug. **Figure 9.2.7** is a summary of the main features of the video interview.

#### Discovery research: 2 years
- A promising drug is identified

#### Preclinical trials: 1–2 years
- In vitro tests to establish pharmokinetic features
- Tissue tests to establish effect on living cells
- For example, strength of ligand receptor binding

#### Clinical trials: 4–7 years
- Animal studies to establish efficacy on a living organism and toxicity
- Clinical trials:
  - Phase 1: healthy volunteers
  - Phase 2: small-scale trials on patients
  - Phase 3: large-scale trials
- For example, LD₅₀ values
- Assessment of methods of administration and calculation of likely safe dose

- Application for licensing the drug
- Marketing

### Activity

Research some specific examples of biological drug testing. Find out details of how aspects such as in vitro and animal testing were carried out. Good examples of drugs to research could be anticancer drugs such as methotrexate and cisplatin, antibiotics such as the penicillins and ACE inhibitors such as captopril.

### Portfolio activity (2.3)

Write a report to describe the sequence of processes that are involved in the biological evaluation of drugs. In your report you should:
- describe the main stages of biological evaluation
- explain the specific data that is obtained by each stage
- give some examples of how these processes have been carried out for named drugs.
4 Abnormal responses

The adverse drug interactions discussed earlier, and the toxic effect of high doses of drugs that you read about at the start of this chapter, are examples of predictable adverse drug reactions (although, as you have seen, there may be considerable variation in exactly how any one individual may respond).

There is also a range of rarer responses (often referred to as idiosyncratic type B reactions) that are much less predictable. Many of these are a result of immune mechanisms and, although rare, are often very serious – it is therefore important that practitioners are aware of these responses.

Immune mechanisms

Immune mechanisms have evolved to destroy pathogens, such as viruses or bacteria, that invade the system. The stage in the mechanism that is relevant to these adverse drug reactions is that which involves the B cells. These are lymphocytes, small white blood cells that recognise foreign molecules (antigens) in blood or tissue, which may have been produced by an invading microorganism.

B cells have antibody molecules on the surface of their cell membrane. Each antibody bonds specifically to one type of antigen. This stimulates the B cell to divide rapidly, forming new cells that secrete antibodies. These antibodies are then involved in a further series of processes that trigger the death of the microorganism.

Allergic reactions

Drug molecules are usually too small to act as antigens by binding to antibody receptors. However, when they bind to certain carrier proteins the resulting complex may display antigenic properties. The drug molecule seems to activate the carrier molecule by changing its structure; molecules that activate carriers in this way are known as haptens.

An activated carrier may then bind to a B cell. In allergic reactions, this binding produces large amounts of a class of antibody known as immunoglobulin E (IgE). This is rapidly distributed around the body and binds to the surface of certain types of cells, including mast cells and basophils. These cells respond to the binding by releasing chemicals such as histamine and cytokine.

Allergic reactions are the result of the action of these chemicals on specific tissues or organs. In the case of drug reactions, these are most likely to be seen as skin rashes, muscle aches or the potentially fatal anaphylaxis. Anaphylaxis, unlike most drug allergies, can occur within minutes of exposure to a drug. See the Drug case study on page 12 for an example of a drug that can cause anaphylaxis.

Key term

Anaphylaxis: A drug allergy that can be recognised by rapid development of skin rash, difficulty in breathing, swelling of face, tongue and lips and a rapid drop in blood pressure.
Drug case study

Penicillin is the general name used for a group of structurally similar antibiotics; it was the first antibiotic to be recognised and used and remains widely prescribed despite the development of bacterial resistance to some of the molecules in the group. However, about 10% of people report an allergic reaction to penicillin, usually rashes, breathing problems or swelling of the face. Even if the reaction seems relatively mild, it is normally advisable not to prescribe penicillin again as there is a chance that the person may develop the much more serious anaphylactic reaction due to the sensitising process.

Because all penicillins are structurally similar, an allergy to one penicillin molecule suggests that there will also be an allergic reaction to all the molecules in the group.

Sensitising

Sensitising is the process by which the allergic reaction to a drug is increased after an initial exposure to it.

It can be readily explained as the first time B cells respond to a drug-based antigen, they clone themselves to produce what are known as ‘memory cells’, which have the specific antibody to the drug-based antigen on the membrane surface. These cells will respond to any reappearance of the drug with greater speed and potentially cause a more rapid and serious reaction.

Activation and suppression

In the discussion of immune-based adverse reactions above, the focus has been on the consequences of a drug activating the immune systems.

By contrast, some drugs can suppress the immune system. This may be a desirable response – for example, in the treatment of arthritis or to prevent the rejection of a transplanted organ.

If patients are already immunosuppressed, for example, due to cancer treatment or HIV infection, then clearly any drug that further suppresses the immune system must be avoided.

Portfolio activity (2.4)

Use research to write a report to describe how penicillins can cause adverse reactions. In your report you should:

• describe the adverse reaction caused
• explain the biological processes that lead to this reaction.

Checklist

At the end of this section you should be familiar with the following ideas:
✓ abnormal responses are often due to activation of immune mechanisms
✓ some drugs also suppress the immune system.

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