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DRUG DISTRIBUTION, METABOLISM, AND ELIMINATION

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Contents

2.5.4 Maintenance doses and loading doses

2.1 Introduction

After a drug has been administered and absorbed into the systemic circulation, it has to be **distributed** in the blood, to its site of action, where the pharmacodynamic process (mechanism of action, actions in the body) will take place. The drug is then usually **metabolised** and **excreted**. Distribution, metabolism and excretion are discussed in the following chapters. Absorption, distribution, metabolism and excretion are all important determinants of the **plasma levels of drugs**. The plasma levels of drugs are also discussed.

2.2. Drug Distribution

2.2.1 Introduction

Blood is aqueous, and only hydrophilic (water soluble) drugs will dissolve in it. For absorption, most drugs have to be lipid soluble. Lipophilic drugs are transported in the blood attached to proteins.

2.2.2 Protein binding

Plasma proteins, such as albumin and globulin, were not designed to carry drugs, but are quite effective at doing so. Acidic drugs bind to albumin, whereas basic drugs bind to globulin. In the plasma there is equilibrium between the protein-bound and free drug (Figure 2.1).

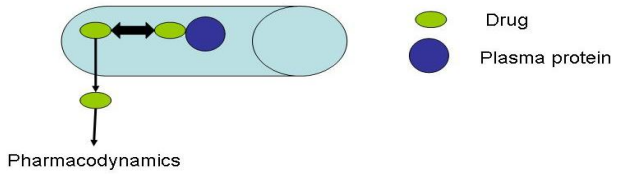

Figure 2.1 Protein binding and distribution (Copyright QUT, Sheila Doggrell)

The bound drug cannot leave the blood stream whereas the free drug can leave the circulation, often to have its pharmacodynamic effect. When free drug leaves the blood vessel, more drug is released from the binding, to maintain the equilibrium. Thus, drug is gradually being released from plasma proteins.

Bilirubin is a yellow breakdown product from red blood cells. Bilirubin binds to albumin. In liver disease, the levels of bilirubin may be high, giving the condition known as jaundice. High levels of bilirubin will also displace drugs from binding to plasma proteins. Thus, the blood levels of free drug may increase in jaundice, with the effect of the drug going from therapeutic to toxic. Thus, in jaundice, the doses of some drugs have to be decreased.

In addition to bilirubin, drugs can compete for the same site on the plasma protein (Figure 2.2).

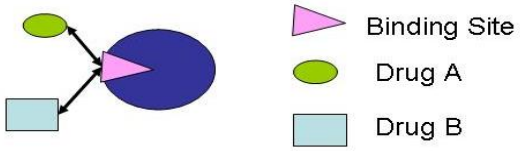

Figure 2.2 Drugs competing for binding site (Copyright QUT University, Sheila Doggrell)

Figure 2.2 shows drugs A and B competing for the same binding site on a plasma protein. **Aspirin** and **warfarin** are examples of drugs that have the same binding site on a plasma protein. Aspirin and warfarin are often used together in cardiovascular disease. Warfarin is used as an anti-coagulant, and the anti-coagulant effect is dependent on the free concentration of warfarin. When aspirin displaces warfarin from their binding site, the free concentration of warfarin will be increased, and there may be too much anti-coagulation, which may lead to haemorrhage. Thus, when aspirin and warfarin are given to a person, it may be necessary to reduce the dose of warfarin.

2.2.3 Factors that modify protein binding and drug distribution?

A **decrease in blood proteins** leads to an **increase** in free drug concentration and effects, and the effects may go from therapeutic to toxic. Blood proteins are decreased by dietary protein insufficiency (malnutrition), liver disease causing decreased synthesis of proteins, and by burns. When there are decreased plasma proteins, it may be necessary to **decrease** the dose of drug, to **decrease** the free concentration of a drug, to go from a toxic effect to a therapeutic effect.

Conversely, when there is an **increase in blood proteins**, there may be a **decrease** in the free drug concentration and the effect of the drug may be lost, as the free plasma concentration goes below that needed for a therapeutic effect. For instance, in multiple myeloma, there is excessive production of immunoglobulin proteins, which bind and inactivate certain drugs. Thus, in multiple myeloma, it may be necessary to **increase** the dose of a drug to **increase** the free concentration, and get a therapeutic effect.

The **lipid solubility** of a drug is an important factor determining distribution. Lipophilic drugs are accumulated in fat tissue, and are only slowly released from fat tissue. For instance, the anti-arrhythmic drug **amiodarone** is very lipophilic, and is accumulated to a great extent in lipids. When the administration of amiodarone is stopped, amiodarone continues to be released out of the fat tissues for weeks. Amiodarone can be a toxic drug. Unfortunately, the toxic effects of amiodarone are slow to reverse, as reversal requires the removal of amiodarone, and that may take weeks.

Another example of a highly lipophilic drug is **marijuana.** After a single use of marijuana, marijuana accumulates in the fat and is slowly released. As a result of this, marijuana can be detected in blood 6 weeks after a single use.

2.2.4 Blood brain barrier

In the systemic circulation, there are gaps between endothelial cells lining blood vessels (Figure 2.3) and, as the basement membrane is freely permeable, this allows most free water and lipid soluble drugs to move out of the systemic circulation (Figure 2.3).

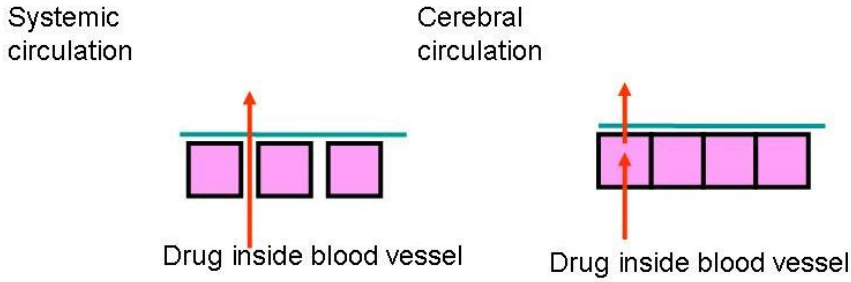

Figure 2.3 Distribution across blood vessels (Copyright QUT University, Sheila Doggrell)

In the cerebral circulation, there are no gaps between the endothelial cells, and this forms a barrier (referred to as the blood brain barrier) mainly to water soluble drugs. Because of this barrier, water soluble drugs cannot get into the brain from the cerebral circulation. Only lipophilic drugs, and drugs that are actively transported, can cross the blood brain barrier. Most drugs used for central nervous system effects are lipophilic. The sedative **diazepam** is a lipophilic drug that moves across lipid membranes into the brain. **L-dopa** is an example of a drug that it is actively transported into brain. The barrier is deficient in chemoreceptor trigger zone, and some drugs act in this zone to exert emetic (vomiting) effects.

For **central nervous system** effects, we need drugs that cross the blood brain barrier. Alternatively, drugs can be administered into the cerebral spinal fluid to bypass the blood brain barrier. For instance, **penicillin** does not cross the blood brain barrier, which is fine when we have a peripheral infection, but not if the infection is within the central nervous system. For central infections, penicillin has to be administered into the cerebral spinal fluid (CSF) by the intrathecal route of drug administration.

For **peripheral** effects, drugs that do not cross the blood brain barrier are preferred. This is because, any central effects of a drug administered for a peripheral effect, may be adverse effects. For instance, the anti-histamine **diphenhydramine** was developed to treat allergy, a peripheral condition, but diphenhydramine crossed the blood brain to have central effects, notably a central sedative effect. Thus, subjects given diphenhydramine for allergy were at risk of falling asleep. The second generation anti-histamines (e.g. **fexofenadine**) were developed to have a reduced ability to cross the blood brain barrier and, consequently, do not exert a sedative effect. Presently, only the second generation anti-histamines are used to treat allergy, and diphenhydramine has been developed as a mild sedative.

2.2.4 Volume of distribution

The **volume of distribution** of a drug or the (apparent) volume of distribution, as it is sometimes called, is not a real distribution, but a parameter that is useful in determining whether **haemodialysis** can be used to rid the body of a particular drug or whether a **loading dose of a drug** is necessary (loading doses are discussed in chapter 6.4). The (apparent) volume of distribution Vd is defined as the volume of fluid required to contain the total amount of drug in the body, at the same concentration as in the plasma. The volume of distribution will be calculated for us when the drug is first developed. Thus, we don't need to know how to calculate it, but we do need to know how to interpret it. For instance, compare Drugs A and B, each administered at 100 mg. They may have different distributions and therefore different volumes of distribution. If after administration Drug A has a plasma level

of 20 mg/ml, and Drug B has a plasma level of 2 mg/ml – it is obvious that Drug B is more widely distributed than Drug A. That is, more of Drug B is distributed outside of the plasma. For Drug A, V_d is 100 mg/20 mg = 5 L, and for Drug B, V_d is 100 mg/2 mg = 50 L.

The plasma volume in a 70 kg adult = 3L (i.e. ~0.04 L/kg). Any drug that is confined to plasma will have similar volume of distribution to the plasma (0.04 L/kg). Drugs that are evenly distributed throughout body (go everywhere at same concentration as plasma) have a Vd of 0.57 L/kg. Drugs that are accumulated in tissues have a greater volume of distribution.

A low volume of distribution indicates that a drug is largely confined to plasma, and can be removed by haemodialysis. Conversely, drugs with a large Vd will be accumulated in fat or elsewhere, and cannot be removed by haemodialysis, which only removes drugs from blood. For instance, **heparin** is mainly confined to blood, has a Vd of 0.06 L/kg, and can be removed by haemodialysis. Conversely, the antidepressant **nortriptyline** has a Vd of 14 L/kg, due to tissue binding outside of the blood stream, and cannot be removed by haemodialysis. Unfortunately, most lipid soluble drugs e.g. **amiodarone** have high volumes of distribution, due to accumulation in fat tissues, and cannot be removed by haemodialysis.

2.3. Drug Metabolism

2.3.1 Introduction

As we discussed previously (Section 2.2), absorption from the gastrointestinal tract is best for lipid soluble drugs. Lipid soluble drugs are also readily reabsorbed from the kidney tubule. Thus, lipid soluble drugs are difficult to get rid of, as even when they get into the kidney tubule, they are reabsorbed rather than excreted. Water soluble compounds are readily excreted from the kidney. Thus, for excretion of a drug, it is necessary to turn a lipid soluble drug into a water soluble (hydrophilic) drug, which can then be excreted in the urine. This change from a lipid soluble to a water soluble compound involves metabolism, which usually has two phases, **Phase I and II metabolism**. In addition to increasing water solubility, metabolism usually produces metabolites that are inactive, and thus reduces the activity of the drug.

Our enzyme systems are not designed to metabolise drugs. However, the normal physiological enzyme pathways for metabolism of endogenous compounds (substances found in the body) are used in drug metabolism. The body also has systems for metabolising xenobiotics (substances foreign to the body), as part of the body's defence system. These xenobiotic metabolising enzymes are also used in drug metabolism.

The liver is the main site of metabolism. Because of this, drug metabolism is changed in hepatic insufficiency. However, the liver is not the only site of drug metabolism. In addition to the liver, metabolising enzymes are present in high concentrations in the intestine, nasal mucosa and lung, and these tissues are all capable of metabolising certain drugs. Most of the discussion of metabolism in this chapter is of liver metabolism.

2.3.2 Phase I

The first phase of metabolism is Phase I. Phase I reactions involve common chemical reactions such as oxidation (interaction with an oxygen), reduction (interaction with a hydrogen), and hydrolysis (interacting with water).

The liver has a huge number of metabolising enzymes. The best characterised metabolic pathways are those catalysed by cytochromes, which are haem proteins. The **Cytochrome**

P450 system (CYP) is a superfamily of distinct enzymes, known as CYP1, 2 and 3, with more than 50 haem-containing enzymes identified to date.

The CYPs are found in the endoplasmic reticulum of the liver cell. One of the most important of the CYPs for drug metabolism is CYP3A4. In this nomenclature for CYP3A4, 3 is for the family of enzyme, A for the subfamily, and 4 is the enzyme isoform. The classification of CYP enzymes into families, subfamilies and isoforms is based on the similarities of the genes encoding for them. CYP3A4 is the most abundantly expressed, and is involved in the metabolism of about 50% of clinically used drugs. CYP2D6 and CYP2C8/9 are also commonly involved in drug metabolism. Drug interactions often occur at the level of these metabolising enzymes, and will be discussed in more detail in the section on drug interactions. The levels of these enzymes are subject to induction and inhibition, and the activity of the enzymes may vary with a subject's genetic makeup (see Chapter 11).

2.3.2.1 Induction

When there is **induction** of an enzyme, there is an **increased** rate of metabolism of drugs by that enzyme, and this leads to a **decreased** plasma concentration of drug, so that it may become ineffective. Lowering the concentration of a therapeutic drug may lead to it becoming ineffective. For instance, hyperforin (a component of **St John's Wort**), an over-the-counter medicine for depression, induces CYP3A4. Use of St John's Wort can lead to the failure of **oral contraceptives**, which are metabolised by CYP3A4. To avoid adverse effects, low doses of oral contraceptives are used to prevent conception. When the metabolism of oral contraceptives is increased by St John's Wort, the levels of the oral contraceptives may fall below those needed for contraception, resulting in pregnancy.

Cigarette smoke and charboiled meats induce CYP1A, which is involved in the metabolism of **paracetamol**. Thus, smokers will have lower plasma levels of paracetamol for the same dose as non-smokers. Lowering the levels of paracetamol will lower the pain relief.

An example of **autoinduction** is **alcohol**, where chronic alcohol consumption induces the enzyme CYP2E1, which is involved in its metabolism. This partly explains the tolerance to alcohol that develops with repeated administration, whereby the same dose of alcohol makes a alcohol-naïve person drunk, with little apparent effect on an alcoholic person, who has induced CYP2E1, and greater metabolism of alcohol.

2.3.2.2 Inhibition

Conversely, the plasma levels of drugs may be **increased** when there is **inhibition** of enzymes. Thus, inhibition of enzymes will lead to a decreased rate of metabolism, and increased plasma concentration of drugs. Under these circumstances, a therapeutic drug may become a toxic drug. It was recently discovered that components of **grapefruit juice** are potent inhibitors of CYP3A4, and this can lead to dangerously high levels of the many drugs that are normally metabolised by this enzyme. Consequently, it is advisable not to take drugs at breakfast with a grapefruit or grapefruit juice, as this may lead to drug toxicity.

Ketoconazole, a commonly used anti-fungal agent is a potent inhibitor of CYP3A4. Thus, ketoconazole will increase the plasma concentrations of the drugs metabolised by this CYP, which includes the **anti-HIV viral protease inhibitors**. The anti-HIV viral protease inhibitors have the potential to be quite toxic, especially if their levels are raised.

2.3.3 Phase II: Conjugation

The second phase of drug metabolism is **conjugation**, which is a Phase I metabolite joining to another compound. Conjugation is very important, as this is the phase that increases the water solubility of the drug, which is needed to allow excretion of the drug. The conjugation substates are naturally occurring substances with the most common Phase II conjugation products being **glucuronides** and **sulphates**. Glucuronic acid is a product of glucose metabolism, and conjugation with glucuronic acid forms glucuronide metabolites. In addition to increasing water solubility, conjugation with glucuronic acid has another important function, it inactivates the drug. This is because the glucuronide metabolites are inactivate.

Some glucuronide metabolites are excreted by the kidney in the urine. However, many glucuronide metabolites are transported in the bile to the gastrointestinal tract and undergo **enterohepatic** recycling (Figure 2.4). In addition, some glucuronide metabolites are partly excreted from the kidney, and partly transported in the bile acid.

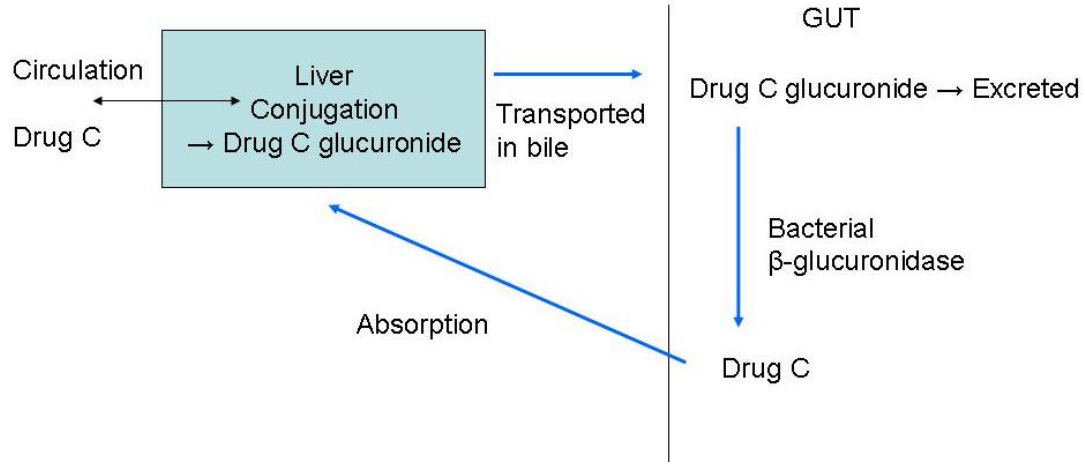

Figure 2.4 Entero-hepatic recycling (Copyright QUT, Sheila Doggrell)

In enterohepatic recycling, Drug C arrives at the liver in the circulation. The metabolism of Drug C involves conjugation with glucuronic acid to form Drug C glucuronide that is transported in the bile to the gastrointestinal tract. Once in the gastrointestinal tract, some of the glucuronide is excreted in the faeces, and some of it may be deconjugated by the bacterial enzyme β-glucuronidase to yield back the active Drug C, that can be **reabsorbed**, and taken to the liver, with some of the active drug **re-entering the circulation**.

Many glucuronides undergo this recycling, and this alters their kinetics (the relationship between plasma concentration and time). The plasma levels may be higher than expected because the drug is being recycled. To counter this, the dose of a drug may need lowering. An example of a drug that undergoes this recycling is **glicazide**, which is used in the treatment of type 2 diabetes. As type 2 diabetes is very common among indigenous Australians, it was of interest to determine whether there were any genetic differences in the recycling of glicazide by Caucasians and indigenous Australians. It was found that there is a slight difference, 30% of the dose in Caucasians is recycled compared to 20% in the indigenous group. Theoretically, this means that for the same dose, the plasma levels could be lower in the indigenous group meaning the the glycaemic control might be slightly lower.

When antibiotics are administered they kill the good as well as the bad (disease causing) bacteria. By killing the good bacteria in gut, antibiotics inhibit bacterial enzyme β-glucuronidase, which inhibits the enterohepatic recycling. Without this recycling of a

glucuronide, plasma drug levels may be lowered, and the drug may become ineffective. For instance, **oral contraceptives** undergo enterohepatic recycling, and with antibiotic use, the plasma levels are reduced which may lead to the preparations providing less contraceptive benefit. This could result in unplanned/unwanted pregnancy..

2.3.4 First pass metabolism and bioavailability

The relationship between first pass metabolism and bioavailability has been discussed previously (Chapter 1), and is only discussed briefly here. Drugs with extensive first pass liver metabolism have poor bioavailability after oral administration. An example of a drug that undergoes extensive first pass liver metabolism is **glyceryl trinitrate** (nitroglycerin), which is used in the treatment of angina. Due to this metabolism, glyceryl trinitrate has to be administered by other routes of administration. Glyceryl trinitrate is used sublingually.

When drugs have considerable first pass liver metabolism, but a proportion still gets to the systemic circulation, it may be possible to increase the dose of drug, to increase the amount of drug that reaches the systemic circulation. This is the case with the painkillers **morphine** and **pethidine**. Large doses of the anti-Parkinson's drug **L-dopa** are also required to produce effective plasma levels of L-dopa.

In **liver disease**, the metabolism of certain drugs may be inhibited, increasing bioavailability. With increased bioavailability, there will be increased effects of a drug. Indeed the plasma levels maybe increased enough to cause toxic effects. Thus, in liver disease, it may be necessary to decrease the doses of drugs metabolised by the liver.

2.3.5 Prodrugs

Prodrugs are pharmacologically inactive drugs that have active metabolites. They are designed so that the maximum amount of active drug reaches the relevant site of action to have the required pharmacodynamic effect. An example of a prodrug is **enalaprilat**. Enalaprilat is a potent inhibitor of angiotensin converting enzyme (ACE), and ACE inhibitors are commonly used in cardiovascular disease. However, it would be pointless to administer enalaprilat orally, as it is not absorbed after oral administration. To circumvent this, the pharmacological inactive prodrug **enalapril** is used. Enalapril is absorbed and has an oral bioavailability of ~60%. **Enalapril** is converted by esterases in the liver to enalaprilat, which is the beneficial ACE inhibitor.

2.3.6 Pharmacologically active metabolites

Some drugs produce **pharmacologically active metabolites**. **Morphine** is a pharmacologically active metabolite of heroin. Morphine acts as an agonist at a particular binding site, the opioid μ-receptors, to cause pain relief. Stimulation of the opioid μ-receptors also underlies the euphoric effects of morphine, and gives its potential for abuse. When morphine is given orally, it undergoes extensive first pass liver metabolism, which lowers the concentration. Morphine only enters the brain slowly. Thus, only low concentrations reach the brain to have an effect.

Heroin is diacetylmorphine, and is more lipid soluble than morphine. Thus, heroin enters the brain more readily than morphine. Once, in the brain, heroin is metabolised to morphine, which gives the pain relief and euphoria. For the same dose, much higher levels of morphine in the brain can be obtained with heroin than morphine. This is a key factor for opioid addicts, who prefer heroin to morphine as their drug of abuse.

2.3.7 Pharmacological toxic metabolites

In addition to the metabolites of drug being therapeutic, metabolites may be toxic. **Paracetamol** is considered by many to be a relatively safe drug. It is considered safe enough to be sold without a prescription. Normally most of the paracetamol is conjugated and excreted in urine (Figure 2.5).

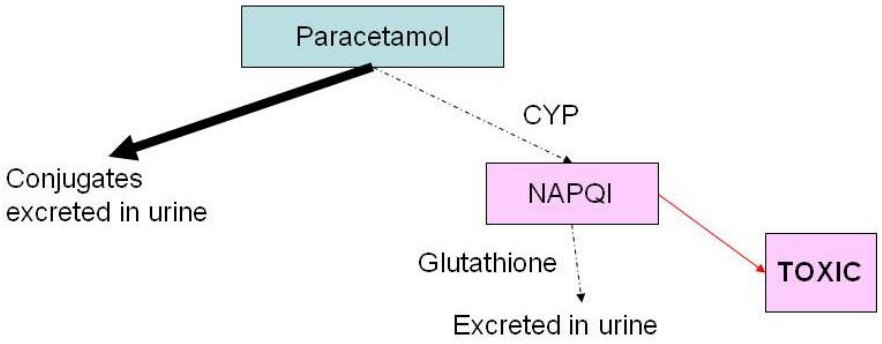

Figure 2.5 Metabolism of paracetamol (Copyright QUT, Sheila Doggrell)

However, a small amount of paracetamol is metabolised by the CYP enzyme system to NAPQI. NAPQI is potentially very toxic to the liver. Fortunately small amounts of NAPQI, in the presence of glutathione, are readily excreted in the urine. Thus, normally, we do not observe toxicity with paracetamol. However, when high doses of paracetamol are administered, the glutathione gets used up, NAPQI levels build up, and become toxic. The main feature of paracetamol poisoning is liver failure. Paracetamol poisoning will be discussed further under treatment of poisoning.

2.4. Drug Elimination

2.4.1 Introduction

The most common way from administration of drug to elimination is by liver metabolism and kidney excretion (Figure 2.6). After oral administration, drugs are taken from the gastrointestinal tract in the circulation for metabolism in the liver.

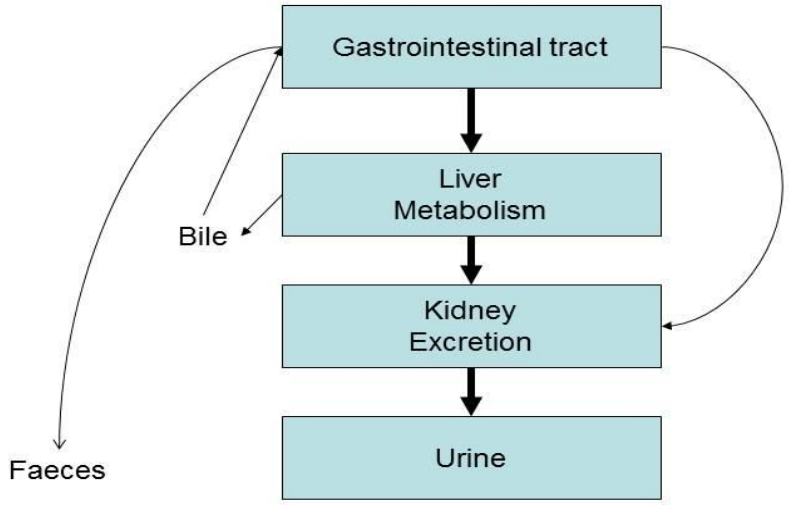

Figure 2.6 Drug Elimination (Copyright QUT, Sheila Doggrell)

Drugs administered by other routes (e.g. sublingual, via injection) also end up in the circulation being carried to the liver for metabolism. After metabolism in the liver, the metabolites are carried in the circulation to the kidney for excretion in the urine. A few drugs are excreted without metabolism. Some drug metabolites are transported in the bile to the gastrointestinal tract, where they may be recycled or eliminated in the faeces.

2.4.2 Kidney

2.4.2.1 Introduction

The kidney is the most important site for excreting drugs. Drugs are eliminated from the body either after conversion to metabolites that are excreted, or they are excreted unchanged.

Kidney function and drug excretion varies with the **life cycle**. When renal function is low or impaired, the excretion of drugs may be reduced, leading to a build up of drug and toxicity. For instance, **renal function** is low in the neonate but matures rapidly in the first few months. This means that neonates may need very small doses, even measured as per kilogram, compared to older people. After maturation, kidney function declines about 1% per year in adulthood. Thus, older-adults (≥ 65 years) may have functional kidney impairment, and require small doses of drugs that undergo excretion from the kidney than the doses used in younger adults.

The first step in excretion from the kidney is glomerular filtration. Drugs are delivered to the kidney in the blood stream, and free drug (water soluble or free fraction of lipid soluble drugs), with the exception of macromolecular substances (**heparin**), freely diffuse into glomerular filtrate. Drugs bound to albumin (e.g. **warfarin**) are held back. Free warfarin and most other drugs/drug metabolites are freely filterable. Some drugs are actively secreted into the kidney tubules.

2.4.2.2 Secretion and Reabsorption

In the adult there are about a million kidney tubules. In these tubules, movement out of the tubule into the interstitial fluid, and, hence, to the blood is known as reabsorption. Movement of substances into the tubules is known as secretion (Figure 2.7).

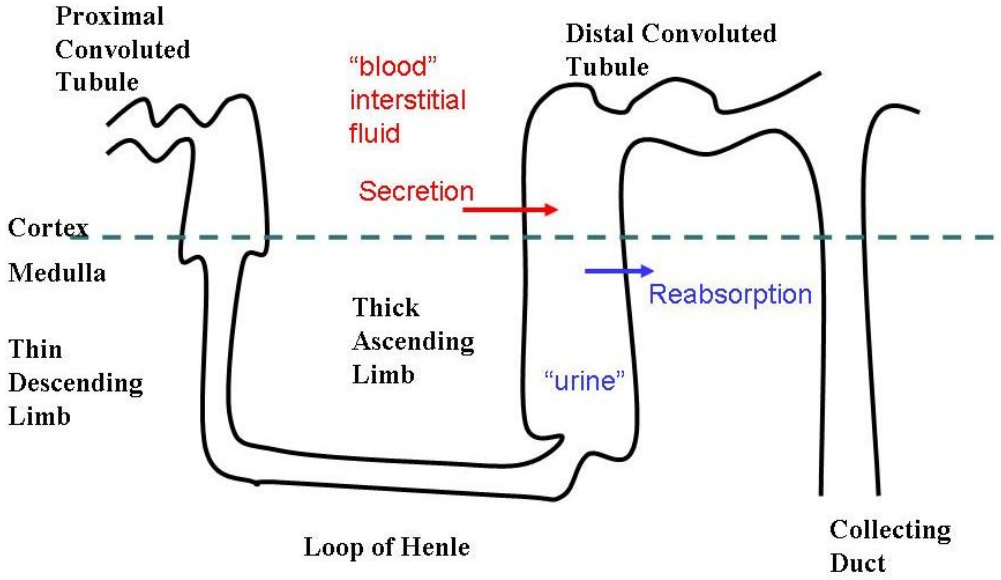

Figure 2.7 Reabsorption and secretion from kidney tubule (Copyright QUT, Sheila Doggrell)

Lipid soluble drugs are readily reabsorbed, so they will continue to be recycled back into circulation. It is only when drugs are water soluble that they remain in the kidney tubule to be excreted.

Endogenous compounds that are positively charged (choline, dopamine) are actively secreted into the proximal tubule using transporters. Many positively charged drugs can be secreted on these transporters (e.g. **ranitidine**), and are excreted following active transport into the urine. Similarly, endogenous compounds that are negatively charged are also secreted into the proximal tubule via transporters, and drugs can use this transporter. Drugs secreted using this transporter include the ACE inhibitor **captopril**.

The drug **probenecid** has two distinct actions on the kidney. The first action is related to uric acid. Uric acid (one of the body's waste products) is actively reabsorbed from the kidney tubule, and an excessive accumulation of urate in the plasma leads to gout. The pain of gout is due to crystals of urate in the joints. Some drugs used to treat gout are known as uricosuric agents. The uricosuric agents (e.g. probenecid) inhibit the reabsorption to promote the excretion of urate, and prevent the accumulation of urate in joints. The second action of probenecid relates to **penicillin** levels. Penicillin is rapidly eliminated from the body, as 90% of penicillin is secreted into the proximal tubule, and excreted. Thus, after administration, the levels and effectiveness of penicillin declines rapidly. However, this can be inhibited by probenecid. Thus, probenecid can be used to increase and prolong the plasma levels of penicillin, to increase the effectiveness of penicillin.

2.4.2.3 Renal insufficiency

In renal insufficiency, (e.g in neonates, and with age-related renal impairment), the duration of action of drugs excreted unchanged from the kidney is prolonged. Examples of drugs

excreted unchanged by the kidney include the **aminoglycoside** antibiotics and **digoxin**. The levels of these drugs may increase in renal insufficiency and produce toxicity. Both of these drugs have a small **therapeutic window**, which means that the concentrations that cause toxicity effects are only slightly above the concentrations that cause a therapeutic effect. The toxicity with aminoglycosides includes ototoxicity (ringing in ears to deafness). Digoxin is used to increase the force of the heart beat in heart failure, and has a small therapeutic window, with toxicity including cardiac arrhythmias. When renal excretion is impaired, it may be necessary to decrease the dose of these drugs and/or increase the dose interval.

Clearance is term given to the combination of metabolism and excretion of a drug. When a drug is metabolised by the liver and the metabolite is excreted via thekidney, renal insufficiency can lead to increased plasma concentrations and adverse effects. Thus, we need to lower doses when there is kidney insufficiency. But how do we know when there is renal insufficiency? We assess kidney function.

Kidney function is assessed from the **creatinine clearance**. Creatinine clearance is the removal of creatinine from the body. Creatinine is natural metabolite of creatine (found in muscle). The properties that make creatinine ideal for assessing kidney function are that creatinine has a steady level in the blood and is freely filtered by the kidney. Thus, with normal function, the plasma and urine levels of creatinine will be similar. In kidney insufficiency plasma creatinine levels are increased, and urine levels are decreased.

When creatinine clearance is inhibited, this indicates renal insufficiency, and that it may be necessary to decrease the dose of drug to avoid toxicity. This can occur with **morphine** in renal insufficiency. An important metabolite of morphine is **morphine-6-glucuronide**, which has similar pharmacological actions to morphine. Morphine-6-glucuronide is excreted from kidney. In renal insufficiency, morphine-6-glucuronide builds up and increases efficacy (pain relief). Unfortunately, increased levels of morphine-6-glucuronide also lead to an increased likelihood of adverse effects, such as respiratory depression. In elderly patients, lower doses of morphine are used partly to compensate for loss of kidney function

2.4.3 Other routes of excretion

Anaesthetic gases are administered by inhalation, and are also excreted from the lung.

Some drugs are excreted in breast milk, and the excreted drugs are a source of unwanted effects in the nursing infant. For instance, **morphine** and other lipid soluble drugs are excreted in breast milk. While it is best to avoid all drugs during breast feeding, there are some breast feeding women who need to take medications. Epileptic mothers may have to continue their medication. Some of the older anti-epileptic drugs e.g. **diazepam**, are known to get into breast milk and should be avoided during breast feeding. There is little information about whether the newer agents get into breast milk, but it is considered that the levels are likely to be too low to have effects in the new-born.

2.5. Blood levels

2.5.1 Introduction

When using drugs as therapeutics, the aim is to produce a specific effect. In most cases, to achieve this it is necessary to get the drug into the plasma at concentrations high enough to produce the effect. However, it is also important not to administer too much drug, as this could lead to a range of non-specific toxic effects. As can be seen in Figure 2.8, the ideal plasma concentration range is between the minimum concentration required to be effective

(minimum effective concentration or MEC) and the concentration, above which toxic effects are seen (minimum toxic concentration).

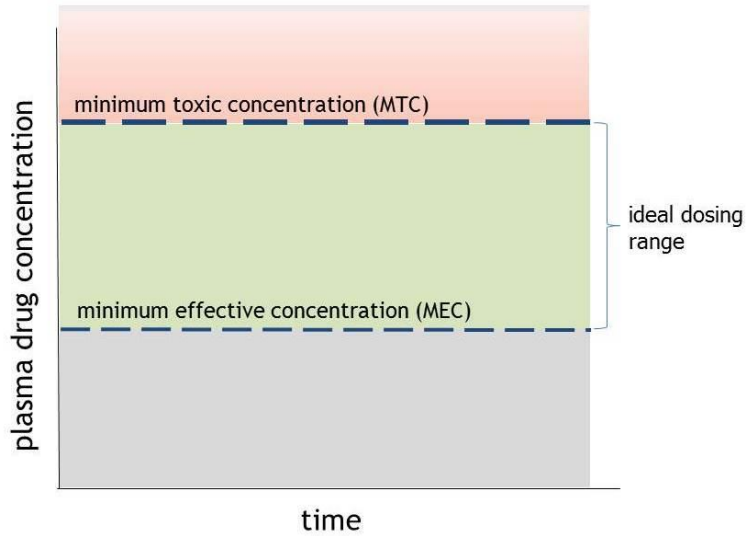

Figure 2.8 Minimum effective and toxic concentrations (Copyright Monash University, Liz Davies)

Graphs are used to describe the relationship between blood levels of drugs over time. From these graphs, we can learn things about drugs that help us to determine how to use them in people.

2.5.2 Elimination half-life

The **elimination half-life** is the time from the maximum concentration to half maximum concentration. The elimination half-life is dependent on the rates of metabolism and elimination of the drug. Thus, slowly metabolised and slowly eliminated drugs will have long half-lives. Whereas, rapidly metabolised and rapidly eliminated drugs will have short half-lives. The half-life is an important determinant of the frequency a drug needs to be administered. Drugs with short half-lives need to be given more often than those with long half-lives.

Provided there is a method for measuring the levels of the drug in the plasma, we can graphically plot the drug concentration against time (Figure 2.9).

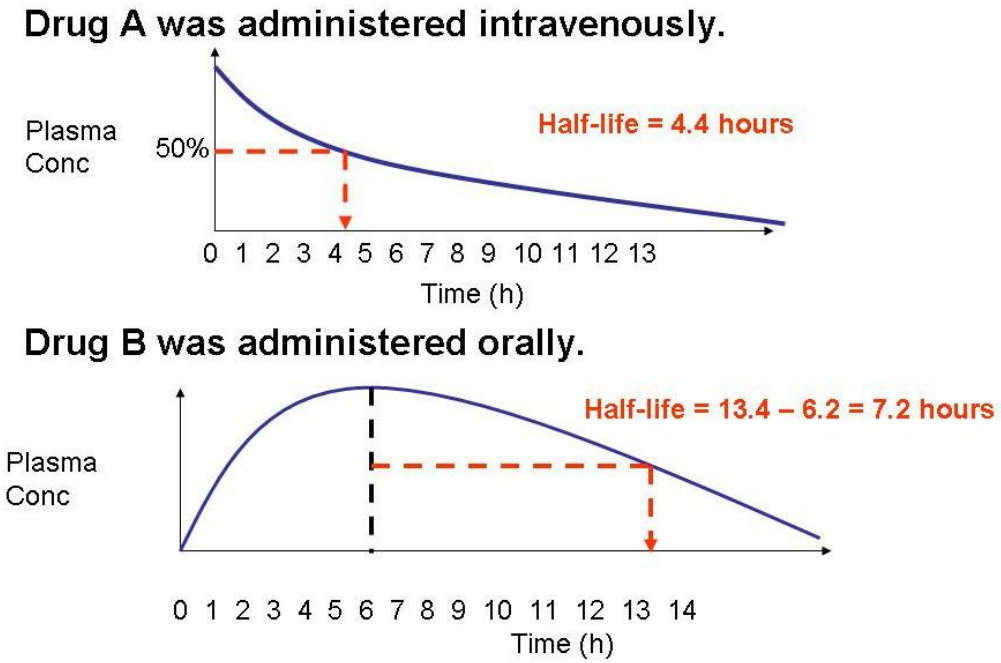

Figure 2.9 Elimination half-life (Copyright QUT, Sheila Doggrell)

In Figure 2.9, Drug A was administered **intravenously**, giving a maximum concentration straight away, and then the concentration diminishes over time, as the drug is metabolised and excreted. The elimination half-life is the time from the maximum concentration to half maximum concentration. Thus, we need to determine the 50% maximal response, and then determine the time from maximal to half-maximal response, which with Drug A is about 4.4 hours. Drug A will have to be administered at least 2 times a day, and maybe more, as it is rapidly metabolised and/or eliminated.

Elimination half-lives can also be determined when drugs are administered **orally**. When Drug B is administered orally, it has to be absorbed into the blood stream, so blood levels rise slowly over time to a maximum. Once again, the elimination half-life is the time from the maximum concentration to half maximum concentration. So we need to estimate the time of the maximal response, which is about 6.2 hours for Drug B. The levels of Drug B have fallen to half-maximal after 13.4 hours. Thus, the elimination half-life is 13.4 – 6.2 hours, which is 7.2 hours. Drug B may be suitable for administration 2 times a day or less, as it is less quickly metabolised and/or eliminated than Drug A

2.5.3 First and zero order kinetics

Graphs of plasma levels against time, can also tell us about the kinetics of the metabolism of the drug (Figure 2.10).

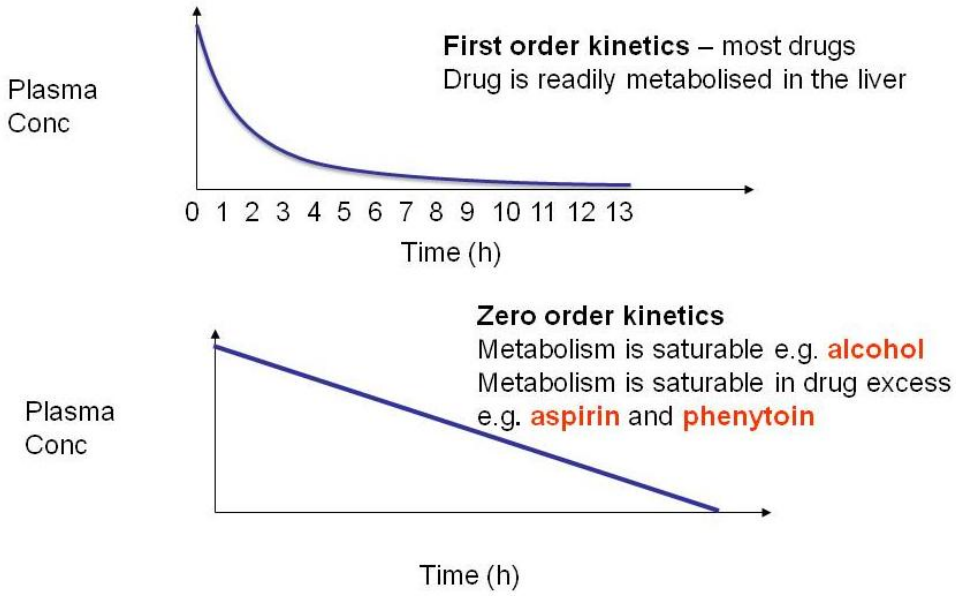

Figure 2.10 Metabolism and Kinetics (Copyright QUT, Sheila Doggrell)

With most drugs, there is a rapid fall in drug levels, as most drugs are readily metabolised, and there is an excess of enzyme available for the metabolism. Thus, the enzyme never becomes saturated with drug. This is known as **first order kinetics** (top, Figure 2.10). In first order kinetics, increasing the concentration of the drug increases the metabolism of the drug. First order kinetics is also observed with drugs that are eliminated unchanged.

With some drugs there is a limited amount of enzyme available to metabolise the drug, and when that limit is reached, metabolism occurs at a constant rate. Thus, the enzyme becomes saturated with drug. This is known as **zero order kinetics**, and is seen as a straight line on the graph (bottom, Figure 2.10). In zero order kinetics, increasing the concentration of drug above a certain point does not increase the rate of metabolism. The best known example of zero order kinetics is **alcohol**. There are no notable examples of therapeutic drugs that have saturable metabolism and zero order kinetics. However, some therapeutic drugs taken in excess can have saturable kinetics. Examples include **aspirin** and the anti-epileptic drug **phenytoin**.

2.5.4 Minimum effective and steady-state concentrations

The **Minimum Effective Concentration** (MEC) is the minimum plasma concentration required for the drug to be effective. When we use drugs, we want to use the appropriate dose and dosing interval to achieve plasma concentrations about the MEC to give an ongoing beneficial effect.

The **steady-state concentration** is a reasonably even concentration achieved with repeat dosing or continued infusion, which gives a continued beneficial effect.

2.5.5 Maintenance doses and loading doses

A **maintenance dose** is a small, fixed dose. When you use maintenance doses, it may take long time to reach the minimum effective concentration, as the plasma concentration only slowly builds up to reach and then exceed the minimum effective concentration (top, Figure

2.11). This is an inappropriate way to administer drugs in serious conditions or emergency situations, where you need the drug to be effective immediately.

With some drugs, especially those with a large volume of distribution, it may be necessary to give a **loading dose** (a big dose) initially to get above the minimum effective concentration and get the beneficial effect quickly. In such situations, a loading dose is used to reach the minimum effective concentration, and then maintenance doses are given to maintain the minimum effective concentration (bottom, Figure 2.11). With a loading dose, the minimum effective concentration is reached much quicker than using the maintenance dose.

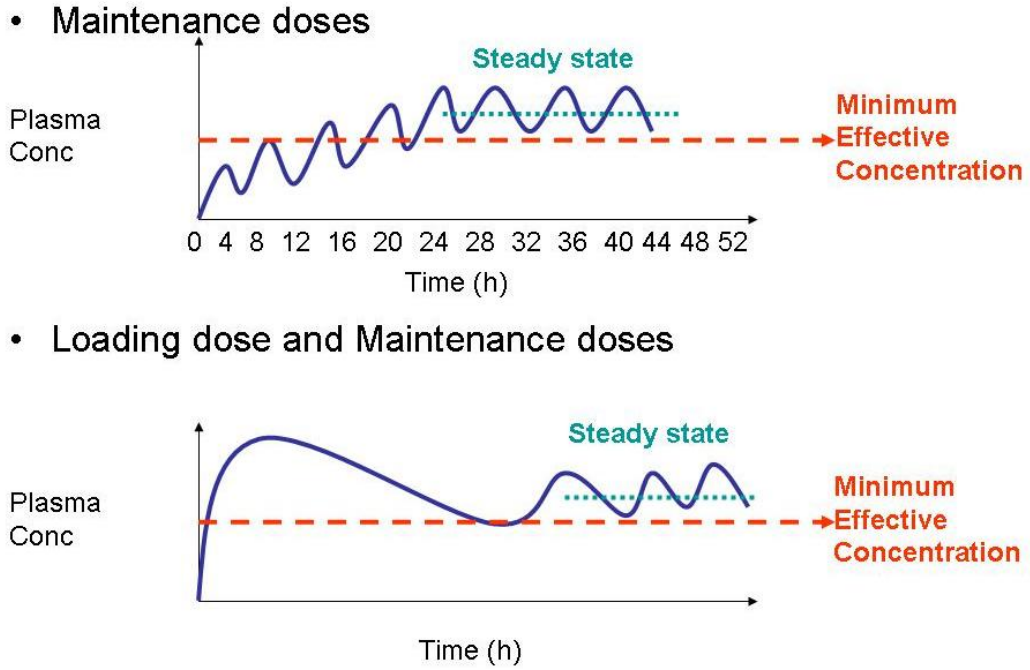

Figure 2.11 Maintenance doses and loading dose (Copyright QUT, Sheila Doggrell)

An example of a drug that is used with a loading dose and maintenance doses is the anti-platelet drug clopidogrel. Intravenous **clopidogrel** is given as a loading dose in percutaneous coronary intervention to prevent clotting straightaway, and this is followed by oral maintenance doses to prevent coagulation, as the subject recovers from the surgery.

Steady-state concentrations are eventually reached with both maintenance and loading/maintenance dosing (Figure 2.11).