1 Introduction

1.1 Therapeutic window

1.1.1 Introduction

It has been said that if a drug has no side effects, then it is unlikely to work. Drug therapy labours under the fundamental problem that usually every single cell in the body has to be treated just to exert a beneficial effect on a small group of cells, perhaps in one tissue. Although drug-targeting technology is improving rapidly, most of us who take an oral dose are still faced with the problem that the vast majority of our cells are being unnecessarily exposed to an agent that at best will have no effect, but at worst will exert many unwanted effects. Essentially, all drug treatment is really a compromise between positive and negative effects in the patient. The process of drug development weeds out agents that have seriously negative actions and usually releases onto the market drugs that may have a profile of side effects, but these are relatively minor within a set concentration range where the drug’s pharmacological action is most effective. This range, or ‘therapeutic window’ is rather variable, but it will give some indication of the most ‘efficient’ drug concentration. This effectively means the most beneficial pharmacodynamic effects for the minimum side effects.

The therapeutic window (Figure 1.1) may or may not correspond exactly to active tissue concentrations, but it is a useful guideline as to whether drug levels are within the appropriate range. Sometimes, a drug is given once only and it is necessary for drug levels to be within the therapeutic window for a relatively brief period, perhaps when paracetamol (acetaminophen) is taken as a mild analgesic. However, the majority of drugs require repeated dosing in time periods which range from a few days for a course of antibiotics, to many years for anti-hypertensives and antithyroid drugs. During repeated intermediate and long-term dosing, drug levels may move below or above the therapeutic window due to events such as patient illness, changes in diet or co-administration of other drugs. Below the lowest concentration of the window, it is likely that the drug will fail to work, as the pharmacodynamic effect will be too slight to be beneficial. If the drug concentration climbs above the therapeutic window, an intensification of the drug’s intended and unintended (off-target) pharmacodynamic actions will occur. If drug levels continue to rise, irreversible damage may occur which is usually described by the word ‘toxicity’. To some extent, every patient has a unique therapeutic window for each drug they take, as there is such huge variation in our pharmacodynamic drug sensitivities. This book is concerned with what systems influence how long a drug stays in our bodies.

Human Drug Metabolism 2E, Michael D. Coleman
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INTRODUCTION

Figure 1.1 The ‘therapeutic window’, where drug concentrations should be maintained for adequate therapeutic effect, without either accumulation (drug toxicity) or disappearance (drug failure). Such is human variation that our personal therapeutic windows are effectively unique for every drug we take.

Whether drug concentrations stay in the therapeutic window is obviously related to how quickly the agent enters the blood and tissues prior to its removal. When a drug is given intravenously, there is no barrier to entry, so drug input may be easily and quickly adjusted to correspond with the rate of removal within the therapeutic window. This is known as ‘steady state’, which is the main objective of therapeutics. The majority of drug use is by other routes such as oral or intramuscular rather than intravenous, so there will be a considerable time lag as the drug is absorbed from either the gastro-intestinal tract (GIT) or the muscle, so achieving drug levels within the therapeutic window is a slower, more ‘hit and miss’ process. The result from repeated oral dosing is a rather crude peak/trough pulsing, or ‘sawtooth’ effect which you can see in the diagram (Figure 1.1). This should be adequate, provided that the peaks and troughs remain within the confines of the ‘therapeutic window’.

1.1.2 Therapeutic index

Drugs vary enormously in their toxicity and the concentrations at which one drug might cause potentially lethal effects might be 10 or 100 times lower than a much less toxic drug. A convenient measure for this is the ‘therapeutic index’. This has been defined as
the ratio between the lethal or toxic dose and the effective dose that shows the normal range of pharmacological effect.

In practice, a drug (such as lithium) is listed as having a narrow TI if there is less than a twofold difference between the lethal and effective doses, or a twofold difference in the minimum toxic and minimum effective concentrations. Back in the 1960s, many drugs in common use had narrow TIs, such as barbiturates, that could be toxic at relatively low levels. Over the last 30 years, the drug industry has aimed to replace this type of drug with agents with much higher TIs. This is particularly noticeable in drugs used for depression. The risk of suicide is likely to be high in a condition that takes some time (often weeks) to respond to therapy. Indeed, when tricyclic antidepressants (TCAs) were the main treatment option, these relatively narrow TI drugs could be used by the patient to end their lives. Fortunately, more modern drugs such as the SSRIs (selective serotonin reuptake inhibitors) have much higher TIs, so the risk of the patient using the drugs for a suicide attempt is greatly diminished. However, there are many drugs (including the TCAs to a limited extent), which remain in use that have narrow or relatively narrow TIs (e.g. phenytoin, carbamazepine, valproate, warfarin). Therefore the consequences of accumulation of these drugs are much worse and happen more quickly than drugs with wide TIs.

1.1.3 Changes in dosage

If the dosage exceeds the rate of the drug’s removal, then clearly drug levels will accumulate and depart from the therapeutic window towards toxicity. If the drug dosage is too low, levels will fall below the lowest threshold of the window and the drug will fail to work. If a patient is established at the correct dose that does not change, then this is the oral version of ‘steady state’. So, theoretically, the drug should remain in its therapeutic window for as long as therapy is necessary unless other factors change this situation.

1.1.4 Changes in rate of removal

The patient may continue to take the drug at the correct dosage, but drug levels may drop out of, or exceed, the therapeutic window. This could be linked with redistribution of the drug between bodily areas such as plasma and a particular organ, or protein binding might fluctuate; however, the major factor in the maintenance of drug levels within the therapeutic window is the rate of removal and/or inactivation of the drug by bodily processes.

1.2 Consequences of drug concentration changes

If there are large changes in the rate of removal of a drug, then this can lead in extremis to severe problems in the outcome of the patient’s treatment: the first is drug failure, whilst the second is drug toxicity (Figure 1.2). These extremes and indeed all drug effects are directly related to the blood concentrations of the agent in question.
1.2.1 Drug failure

Although it might take nearly a decade and huge sums of money to develop a drug that is highly effective in the vast majority of patients, the drug can only exert an effect if it reaches its intended target in sufficient concentration. There may be many reasons why sufficient concentrations cannot be reached. Drug absorption may have been poor, or it may have been bound to proteins or removed from the target cells so quickly it cannot work. This situation of drug ‘failure’ might occur after treatment has first appeared to be successful, where a patient becomes stabilized on a particular drug regimen, which then fails due to the addition of another drug or chemical to the regimen. The second drug or chemical causes the failure by accelerating the removal of the first from the patient’s system, so drug levels are then too low to be effective. The clinical consequences of drug failure can be serious for both for the patient and the community. In the treatment of epilepsy, the loss of effective control of the patient’s fits could lead to injury to themselves or others. The failure of a contraceptive drug would lead to an unwanted pregnancy and the failure of an antipsychotic drug would mean hospitalization for a patient at the very least. For the community, when the clearance of an antibiotic or antiparasitic drug is accelerated, this causes drug levels to fall below the minimum inhibitory concentration, thus selecting drug-resistant mutants of the infection. Therapeutic drug failure is usually a gradual process, where the time frame may be days before the problem is detected (Figure 1.2).
1.2.2 Drug toxicity

If a drug accumulates for any reason, either by overdose or by a failure of drug removal, then serious adverse reactions will result. A reduction in the rate of removal of the drug from a system (often due to administration of another drug), will lead to drug accumulation. Toxicity can be an intensification of a drug’s therapeutic action, or an unrelated damaging effect on a tissue or organ system. If the immunosuppressive cyclosporine is allowed to accumulate, severe renal toxicity can lead to organ failure. Excessive levels of anticonvulsant and antipsychotic drugs cause confusion and drowsiness, whilst the accumulation of the antihistamine terfenadine, can lead to lethal cardiac arrhythmias. In contrast to drug failure, drug toxicity may occur much more rapidly, often within hours rather than days.

1.3 Clearance

1.3.1 Definitions

The consequences for the patient when drug concentrations either fall below the therapeutic window or exceed it can be life threatening. The rate of removal of the drug from the body determines whether it will disappear from, or accumulate in the patient’s blood. A concept has been devised to understand and measure rate of removal; this is known as ‘Clearance’. This term does not mean that the drug disappears or is ‘cleared’ instantly.

The definition of clearance is an important one that should be retained:

*Clearance is the removal of drug by all processes from the biological system.*

A more advanced definition could be taken as:

*A volume of fluid (plasma, blood or total body fluid) from which a drug is irreversibly removed in unit time.*

Clearance is measured in millilitres of blood or plasma per min (or litres per hour) and is often taken to mean the ‘clearance’ of the drug’s pharmacological effectiveness, which resides in its chemical structure. Once the drug has been metabolized, or ‘biotransformed’, even though only a relatively trivial change may have been effected in the structure, it is no longer as it was and products of metabolism, or metabolites as they are known, often exert less or even no therapeutic effect. Whether or not they retain some therapeutic effect, metabolites are usually removed from the cell faster than the parent drug and they will eventually be excreted in urine and faeces. There are exceptions where metabolites are as effective as the parent drug (some tricyclic antidepressants, such as desipramine and morphine glucuronides), and there are metabolites that are strangely even less soluble in water and harder to excrete than the parent compound (acetylated sulphonamides), but in general, the main measure of clearance is known as total body clearance, or sometimes, systemic clearance:

\[ Cl_{\text{total}} \]
This can be regarded as the sum of all the processes that can clear the drug. Effectively, this means the sum of the liver and kidney contributions to drug clearance, although the lung and other organs can make some contribution.

For drugs like atenolol or gabapentin, which unusually do not undergo any hepatic metabolism, or indeed metabolism by any other organ, it is possible to say that:

\[ Cl_{\text{total}} = Cl_{\text{renal}} \]

So renal clearance is the only route of clearance for these drugs, in fact it is 100 per cent of clearance.

For paracetamol and for most other drugs, total body clearance is a combination of hepatic and renal clearances:

\[ Cl_{\text{total}} = Cl_{\text{hepatic}} + Cl_{\text{renal}} \]

For ethanol, you will probably already be aware that there are several routes of clearance, including hepatic, renal and the lung, as breath tests are a well-established indicator of blood concentrations.

\[ Cl_{\text{total}} = Cl_{\text{hepatic}} + Cl_{\text{renal}} + Cl_{\text{lung}} \]

Once it is clear what clearance means, then the next step is to consider how clearance occurs.

### 1.3.2 Means of clearance

In absolute terms, to clear something away is to get rid of it, to remove it physically from the system. The kidneys are mostly responsible for this removal, known as elimination. The kidneys cannot filter large chemical entities like proteins, but they can remove the majority of smaller chemicals, depending on size, charge and water solubility. The filtrate eventually reaches the collecting tubules that lead to the ureter and the bladder. As the kidney is a lipophilic (oil-loving) organ, even if it filters lipophilic drugs or toxins, these can easily leave the urine in the collecting tubules and return to the surrounding lipophilic tissues and thence back to the blood. So the kidney is not efficient at eliminating lipophilic chemicals.

One of the major roles of the liver is to use biotransforming enzymes to ensure that lipophilic agents are made water soluble enough to be cleared by the kidney. So the liver has an essential but indirect role in clearance, in that it must extract the drug from the circulation, biotransform (metabolize) it, then return the water-soluble product to the blood for the kidney to remove. The liver can also actively clear or physically remove its metabolic products from the circulation by excreting them in bile, where they travel through the gut to be eliminated in faeces. Bacterial effects on this process can lead to the reabsorption of the metabolite or parent drug into the gut, a process known as enterohepatic recirculation (Chapter 6, section 6.2.9).

The liver has an impressive array of enzymatic systems to biotransform drugs, toxins and other chemical entities to more water-soluble products. However, the ability of the
liver to metabolize a drug can depend on the structure and physicochemical characteristics of the agent, so some drugs are easy for it to clear and some are difficult.

1.4 Hepatic extraction and intrinsic clearance

1.4.1 High extraction drugs

Hepatic extraction is a useful term to measure how easily the liver can process, or metabolize, a given drug or toxin. The term ‘hepatic extraction’ effectively means the difference between the drug level in blood that enters the liver (100 per cent) and the amount that escapes intact and unmetabolized (that is, 100 per cent minus the metabolized fraction).

Extraction is usually termed $E$ and is defined as the extraction ratio, or

$$\text{Extraction Ratio} (E) = \frac{\text{Concentration entering the liver}}{\text{Concentration leaving the liver}} - 1$$

Clinically, most drugs’ hepatic extraction ratios will either be high ($E > 0.7$), or low ($E < 0.3$), with a few agents falling into the intermediate category ($E$ is $>0.3$, but $<0.7$). For high extraction drugs, the particular enzyme system that metabolizes this drug may be present in large amounts and drug processing is very rapid. This often happens if the drug is very similar in structure to an endogenous agent, which is normally processed in great quantity on a daily basis. Hence, the early anti-HIV drug AZT (zidovudine), is a close structural analogue of the DNA constituent thymidine and so possesses a half-life of an hour or less in man. In the case of a high extraction drug, the inbuilt or ‘intrinsic’ ability of the liver to metabolize the drug means that the only limitation in the liver’s ability to metabolize this type of drug is its rate of arrival, which is governed by blood flow.

So, in the case of a high clearance drug, where the liver’s intrinsic ability to clear it is very high:

$$Cl_{\text{hepatic}} = Q (\text{liver blood flow}) \times \text{Extraction ratio } E$$

i.e.

$$Cl_{\text{hepatic}} = QE$$

So, basically, hepatic clearance is directly proportional to blood flow:

$$Cl_{\text{hepatic}} \propto Q$$

During intensive exercise, human liver blood flow can fall temporarily by more than 70%, but during normal day-to-day living, blood flow through the liver does not normally vary that much. This means that a high extraction drug will be cleared at a fairly predictable rate. However, hepatic blood flow can be significantly reduced in old age (Chapter 7, section 7.3.1) and end-stage cirrhotic alcoholism (Chapter 7, section 7.7.7). Patients with impaired cardiac output, either as a result of congestive heart failure or myocardial
infarction, also experience marked reductions in liver blood flow. All these circumstances have been shown to reduce the clearance of high extraction drugs clinically and should be borne in mind during drug dosage determination in these patients.

Many drugs are bound in plasma to proteins such as human serum albumin (HSA) or alpha-1 acid glycoprotein (AAG). HSA usually transports endogenous acidic agents, such as fatty acids, bilirubin and bile acids, although it also binds drugs such as warfarin, ibuprofen and diazepam. The endogenous function of AAG is not fully understood, but may involve modulation of the immune system. AAG will bind basic drugs such as erythromycin and protease inhibitors.

Usually, for any given drug, there is equilibrium between protein-bound and free drug. In effect, high extraction drugs are cleared so avidly, that the free drug disappears into the metabolizing system and the bound pool of drug eventually becomes exhausted. As the protein binding of a high extraction drug is no barrier to its removal by the liver these drugs are sometimes described as undergoing ‘unrestricted’ clearance. Drugs in this category include pethidine (known as meperidine or Demerol in the US), metoprolol, propranolol, lignocaine, nifedipine, fentanyl and verapamil.

You also might see the term ‘intrinsic clearance’ which reflects the inbuilt ability of the liver (independent from other variables like blood flow) to remove a drug; high extraction drugs have a high intrinsic clearance. As mentioned above, the only limitation in clearance for these drugs is how much drug the blood can deliver. If blood flow was to be infinite, then hepatic clearance would be the same as intrinsic clearance.

1.4.2 Low extraction drugs

On the opposite end of the scale \((E < 0.3)\), low extraction drugs are cleared slowly, as the metabolizing enzymes have some difficulty in oxidizing them, perhaps due to stability in the structure, or the low capacity and activity of the metabolizing enzymes. The metabolizing enzymes may also be present only in very low levels. These drugs are considered to be low intrinsic clearance drugs, as the inbuilt ability of the liver to remove them is relatively poor.

If a low extraction drug is not extensively bound to protein (less than 50 per cent bound) then how much drug is cleared is related directly to the intrinsic clearance of that drug. In the case of a low extraction, strongly protein bound drug, then the liver finds clearance even more difficult, as the affinity of drug for the protein is much greater than the liver’s affinity for the drug. The anticonvulsants phenytoin and valproate are both highly protein bound (≈90 per cent) and low extraction drugs and so the amount of these drugs actually cleared by the liver really depends on how much unbound or free drug there is in the blood. This means that:

\[
Cl_{\text{hepatic}} \propto Cl_{\text{intrinsic}} \times \text{fraction unbound}
\]

Therefore, clearance is proportional to the ability of the liver to metabolize the drug \((Cl_{\text{intrinsic}})\) as well as the amount of unbound or free drug in the plasma that is actually available for metabolism. Hepatic blood flow changes have little or no effect on low extraction drug plasma levels, but if the intrinsic ability of the liver to clear a low extraction drug falls even further (due to enzyme inhibition or gradual organ failure), there will
be a significant increase in plasma and tissue free drug levels and dosage adjustment will be necessary. Conversely, if the intrinsic clearance increases (enzyme induction, Chapter 4) then free drug levels may fall and the therapeutic effects of the agent will be diminished.

It is worth noting, that with drugs of low extraction and high protein binding such as phenytoin and valproate, a reduction in total drug levels due to a fall in protein binding (perhaps due to renal problems or displacement by another, more tightly bound drug) will actually have no sustained effect on free drug plasma and tissue levels, as the ‘extra’ free drug will just be cleared or enter the tissues and the bound/unbound drug ratio will quickly re-assert itself. Since the free drug is pharmacologically active and potentially toxic whilst the bound drug is not, it is not usually necessary to increase the dose in these circumstances. The concentration of the free drug has the greatest bearing on dosage adjustment considerations and laboratory assay systems are now routinely used to determine free drug levels with highly bound, low extraction drugs which are therapeutically monitored, such as with phenytoin and valproate. Other examples of low extraction drugs include paracetamol, mexiletine, diazepam, naproxen and metronidazole. The term ‘restrictive’ clearance is also used to describe these drugs, as their clearance is effectively restricted by their protein binding.

1.5 First pass and plasma drug levels

Clearance is the removal of drug from all tissues and usually the liver is seen as the major force in the clearance of drugs. However, this is an oversimplification, as other tissues can clear drugs and in the real world of a drug entering the body, the gut makes a significant contribution to clearance (Figure 1.3). To be absorbed from the gut, the drug must pass through the gut mucosal epithelial cells and enter the hepatic portal circulation, which leads directly to the liver. A drug may diffuse past the membranes of the gut epithelial cells passively, due to its relative lipophilicity or if it is more water soluble, it may require ‘help’ from transporter systems called solute carriers (Chapter 2, section 2.6.2). These transporters normally convey vital nutrients such as amino acids as well as drugs with similar physicochemical characteristics (like some statins). However, once in the gut epithelial cells, a drug can be pumped back out into the lumen by efflux proteins (Chapter 4, section 4.4.7) and/or metabolized by various enzymes in the gut wall cells. In the case of some drugs, this can account for a high proportion of the dose before it reaches the liver. The fraction of the original dose left then enters the liver and following hepatic extraction, most of the dose will have been inactivated. This is particularly apparent with high extraction drugs. This process, where an oral dose is metabolized by various systems, is termed ‘first pass’.

In some drugs, the vast majority of the dose is lost before it reaches the systemic circulation. The amount that actually reaches the plasma can be measured and the amount that was dosed is also known, so an equation can be produced which gives us how much enters the system. This is known as the ‘absolute bioavailability’ of the drug and is termed $F$. It can be defined as

$$F = \frac{\text{Total amount of drug in the systemic circulation after oral dosage}}{\text{Total amount of drug in the systemic circulation after intravenous dose}}$$
Highly extracted drugs are often stated to have a ‘poor bioavailability’. This means that the oral dose required to exert a given response is much larger than the intravenous dose. If the bioavailability is 0.2 or 20 per cent, then you might need to administer about five times the intravenous dose to see an effect orally.

### 1.5.1 Changes in clearance and plasma levels

Consider an extreme example; if the intravenous dose of a poorly bioavailable ($F = 0.2$), narrow TI drug X was 20 mg and the usual oral dose was 100 mg, it is clear that if the whole oral 100 mg were to reach the plasma, the patient would then have plasma levels far in excess of the normal intravenous dose, which could lead to toxicity or death. This could happen if the first pass effect was reduced or even completely prevented by factors that changed the drug’s clearance.

Similarly, if the clearance of the drug was to be accelerated, then potentially none of the 100 mg would reach the plasma at all, so causing lack of efficacy and drug failure.
1.6 Drug and xenobiotic metabolism

From the therapeutic point of view, it is essential to ensure that drug concentrations remain within the therapeutic window and neither drug failure, nor drug toxicity, occur in the patient. To understand some of the factors related to drug metabolism that can influence the achievement of these aims, there are several important points to consider over the next few chapters of this book.

- What are the metabolic or biotransformational processes that can so dramatically influence drug concentrations and therefore drug action?
- How do these processes sense the presence of the drugs and then remove these apparently chemically stable entities from the body so effectively?
- What happens when these processes are inhibited by other drugs, dietary agents and toxins?
- What is the effect of illness, genetic profile and other patient circumstances on the operation of these processes?
- How can these processes of removal of a drug lead to toxicity?
- What were these processes originally designed to achieve and what is their endogenous function?

The next chapter considers the last point and illustrates that in a subject usually termed ‘drug metabolism’, modern drugs are newcomers to an ancient, complex and highly adaptable system that has evolved to protect living organisms, to control instruction molecules and carry out many physiological tasks.