3- Distribution: Compartments and Volume of Distribution

In this chapter we will consider the factors that govern the rate and extent of drug movement between the blood and tissues and introduce a new pharmacokinetic parameter – the Volume of Distribution.

All sections of this chapter are relevant to both drug development and clinical practice.

The rate of distribution and compartments

Figure 3.1 shows drug passing backwards and forwards between blood and a series of different tissues. It is assumed that drug will distribute into and out of tissues at varying rates; these are indicated by the width of the arrows. In the figure, drug moves most rapidly into Tissues 1 and 2 with Tissue 1 being fastest of all. Movement into Tissues 3 & 4 is slow, with Tissue 4 being slowest.

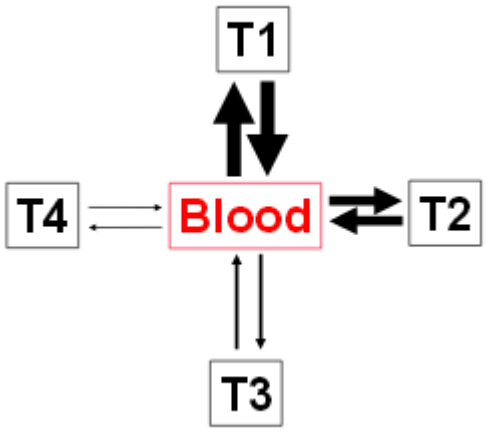

Figure 3.1: Drug moving at varying rates between blood and a series of different tissues.

An exact description of drug handling within the whole body would be immensely complex as it would have to model each tissue separately. To achieve a practically useful model, we make two simplifications. Neither of these is strictly realistic, but they give us access to models that are good enough for practical purposes without undue mathematical complexity.

The two simplifications are:

-We allow for just two rates of distribution – '**Rapid' and 'Slow'**. All tissues are then assumed to belong to **one class** or the other. All the slow ones are assumed to permit drug distribution at one fixed (slow) rate and for all other tissues, distribution occurs at a common (rapid) rate.

-For the 'Rapid' tissues, we consider movement to be instantaneous; as soon as drug arrives in the blood, it is assumed to spread immediately into all the space provided by the 'Rapid' tissues.

For the situation shown in Figure 3.1, blood and Tissues 1 and 2 would be considered as a single space into which drug moves instantly following injection or absorption. Tissues 3 and 4 would form another space into which drug moves at some fixed and relatively slow rate.

The term 'Compartment' is used to describe these aggregations of tissues that are treated as allowing drug to enter at a common rate.

A 'Compartment' is a collective term for all those areas of the body into which a drug distributes at approximately the same rate.

One compartment model

The simplest model allows for instantaneous distribution of drug throughout the blood (and probably to some extent tissues), but this is not then followed by any further slow movement elsewhere. This is shown in Figure 3.2. Drug spreads instantly throughout the blood and Tissues 1 and 2, but never enters other tissues

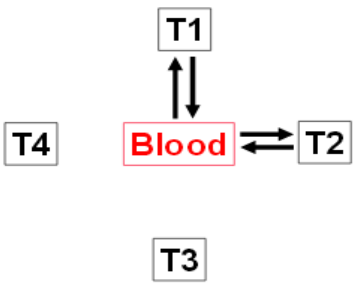

Figure 3.2: Basis of the one compartmental model

The complete ADME process for the one compartmental situation is usually shown in schematic form as in Figure 3.3.

Drug is injected or absorbed into the blood and distributes immediately throughout its range and is eventually eliminated.

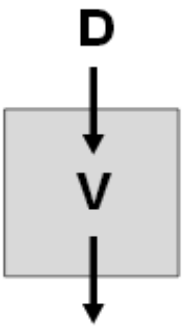

Figure 3.3: Schematic diagram of drug handling with one compartment

Two compartment model

Figure 3.4 shows drug behaviour in a two compartment model. Drug is injected or absorbed and spreads instantly throughout the blood and the rapidly equilibrating tissues T1 & T2 (**First compartment**) and then there is a significant delay while drug enters the rest of the body (**Second compartment**).

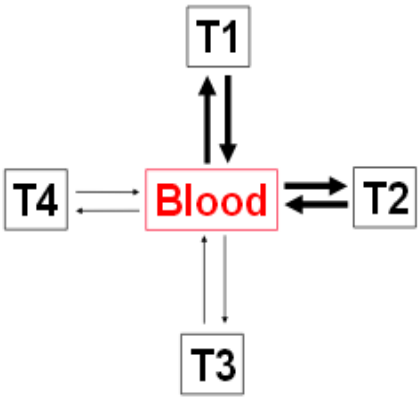

Figure 3.4: Basis of the two-compartmental model

There are **two principal factors** that can influence the rate at which drugs move in and out of tissues. The first is the **polarity** of the drug; **non-polar** drugs undergo passive diffusion easily and so can enter tissues more rapidly than polar ones. The other **major factor** is **blood flow**; where tissues have a rich blood supply, drugs can be delivered and removed quickly, whereas significant delay is unavoidable where

blood flow is sparse. For many drugs, **blood flow is the critical factor**, and for the rest of this chapter, we will focus solely on that, but it should be remembered that polarity can be an issue and we will refer to this at a later point.
It is generally assumed that the rate of drug delivery to and removal from, tissues is governed by **blood flow**.

Notice that the two principal drug eliminating organs (**Liver and kidney**) are both well perfused and therefore form part of the first compartment. When we draw a schematic diagram of a two compartment system, we therefore indicate drug elimination as occurring only from the first compartment.
Figure 3.5 shows drug handling for a two compartment system. Drug is injected or absorbed into the blood (part of the first compartment) and spreads immediately throughout this compartment. There is then slower distribution into the second compartment and from there, back to the first. Elimination is shown occurring exclusively from the first compartment. The second compartment acts as a passive reservoir. The types of tissues forming this compartment (Fat, bone, skin, muscle etc) do not generally significantly metabolize or excrete drugs, so during their stay within this compartment, drugs are unlikely to be eliminated.

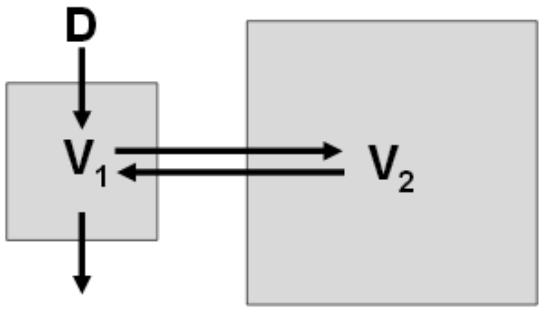

Figure 3.5: Schematic diagram of drug handling with two compartments

The extent of distribution

In the first part of this chapter, we focused on the rate at which drugs enter various parts of the body. In this second section, we are concerned with the Extent of drug movement (i.e. how much of the dose moves out of the blood into the tissues).

Four factors govern the extent to which drugs move out of the blood into tissues:

1. Ability to undergo passive diffusion
2. Binding to macromolecules
3. P-glycoproteins
4. Ion trapping

Ability to undergo passive diffusion

We have already, that most drugs rely on passive diffusion in order to cross biological membranes and hence undergo absorption into the blood. We also saw that the ability to undergo this process depended primarily upon adequate lipid solubility. Similar logic applies to distribution from blood to tissues. Very water soluble molecules will undergo passive diffusion inefficiently and distribute from the blood into tissues either slowly (e.g. **digoxin**) or hardly at all (e.g. gentamicin).

Binding to macromolecules

Drugs cannot undergo passive diffusion while bound to a macromolecule such as a protein or DNA. Take the example of blood **albumin**, which binds a wide range of drugs. The protein molecule is far too water soluble to undergo passive diffusion. Albumin is much larger than most drug molecules and the physical chemistry of a drug-protein complex is dominated by the protein moiety – it is also water soluble and incapable of undergoing passive diffusion. Consequently drugs that are bound to macromolecules are effectively trapped on one side of a biological membrane, unable to distribute to the other side. Figure 3.6 shows drug movement between blood and tissues and the effect of binding to a macromolecule (such as albumin) in blood.

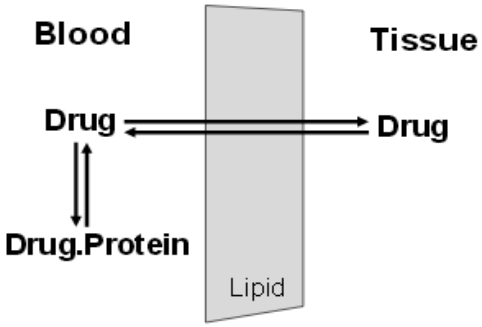

Figure 3.6 : Drug distribution between blood and tissue in the presence of binding to a blood protein

Free (unbound) drug molecules are assumed to be lipid soluble and freely able to move in either direction across the lipid membrane. Drug bound to a blood protein is trapped in the blood. At equilibrium, concentrations of free drug will be equal on both sides of the membrane. However, total drug concentration will be higher in the blood because of the additional protein bound material Figure 3.7 shows the reverse situation, with binding to intracellular macromolecules. Drug has bound to a protein or nucleic acid or possibly been dissolved into lipid within tissue. The result is the opposite of Figure 3.6; there is now a higher total concentration in the tissues than in blood.

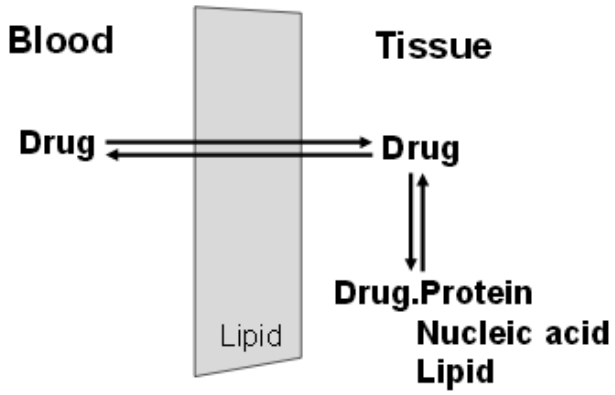

Figure 3.7: Drug distribution between blood and tissue in the presence of binding to a protein etc within tissue

Finally in Figure 3.8, we see what is usually the real situation – binding in both blood and tissues. The outcome will depend upon the relative binding affinity of the blood and intracellular components. For some drugs, plasma binding predominates and the drug will be found primarily in the blood and for others vice versa.

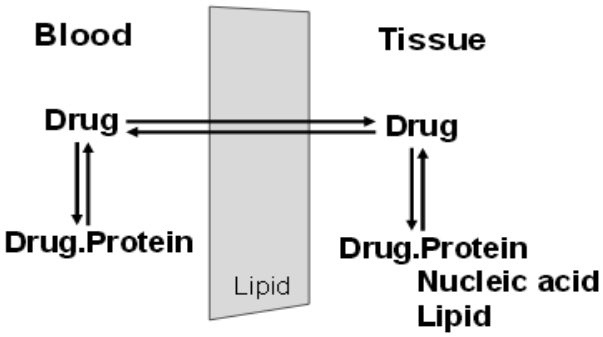

Fig 3.8: Drug distribution between blood and tissue in the presence of binding to macromolecules in both blood and tissues.

P-glycoproteins

We saw how P-glycoproteins in the gut can actively pump drugs across membranes and hence inhibit drug absorption. P-glyoproteins are also present in other parts of the body and have an effect upon drug distribution between blood and tissues.

P-glycoproteins seem to have evolved as a mechanism to protect the body from toxic molecules that may be ingested. The central nervous system (CNS) is particularly sensitive to poisoning and one line of defence consists of P-glycoproteins at the blood brain barrier, which prevent the entry of toxins (and certain drugs) into the CNS.

Ion trapping

Ion trapping arises when an ionisable drug encounters a pH gradient. An example is shown in Figure 3.9.

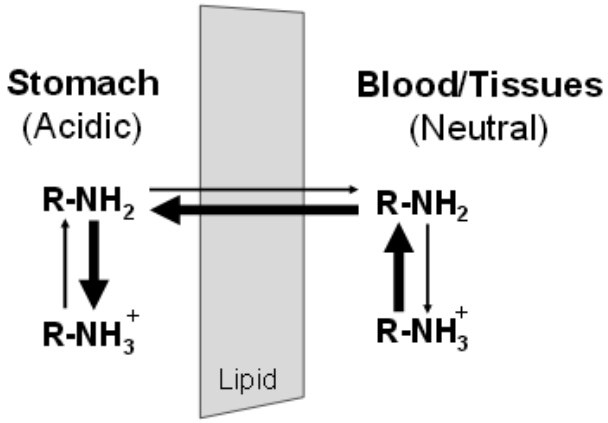

Figure 3.9: Ion trapping of a basic drug in the acidic medium of the stomach

The example in Figure 3.9, assumes that a basic drug contains an ionisable nitrogen atom. The stomach contents are strongly acidic, while blood and tissues are approximately neutral. In its non-ionized form the drug is lipid soluble and able to cross membranes by passive diffusion. However, once ionized it is much more polar and unable to cross.

A sequence of events arises:

- The highly acidic environment within the stomach, causes an extensive shift in the equilibrium between ionized and non-ionized drug towards ionization (Hence the dominant arrow in the appropriate direction).
- The process described above, reduces the concentration of non-ionized drug in the stomach and creates a disequilibrium, with a lower concentration of non-ionized material in the stomach than in the blood.

  Consequently, non-ionized drug moves into the stomach contents.
- This physical movement depletes the concentration of non-ionized drug in the blood, causing a disequilibrium between ionized and non-ionized drug. This is resolved by re-equilibration - the conversion of ionized into non-ionized drug within the blood.

By following the heavy arrows, it can be seen that the overall effect is to transfer drug from the blood into the stomach contents. A practical example of ion trapping is that morphine (an alkaloid) will be found in raised concentrations in stomach contents during an autopsy following overdose.

The opposite effect would be seen with an acidic drug; at equilibrium there would be higher concentrations of drug in the blood **than** in the stomach. The general rule is a kind of 'attraction of opposites'; acidic drugs accumulate in basic environments and basic drugs in acidic ones.

Attraction of opposites: Ion trapping will cause an accumulation of basic drugs in any relatively acidic environment and vice versa

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Volume of distribution

The four factors discussed above will jointly govern the extent to which drug moves out of blood into tissues. Figure 3.10 summarizes the spectrum of possibilities. The figure represents drug concentration by the degree of shading. In (a), nearly all the drug is retained in the blood with very little moving out into the tissues. In (c), we see the opposite pattern, most of the drug having moved into the tissues. Part (b) represents a more balanced outcome.

The ‘Volume of distribution’ is the parameter used to describe the behaviour of a particular drug. A situation such as (a) is conveyed by a small volume of distribution and that in (c) by a large value. The volume of distribution is usually represented by the symbol ‘V’.

The volume of distribution reflects the tendency of a drug to distribute out of the blood into the tissues. A **large volume** implies a strong tendency to distribute into the tissues.

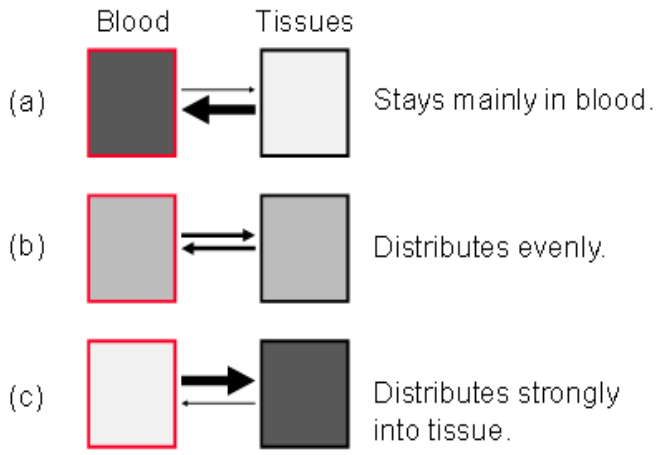

Figure 3.10: The spectrum of possible patterns of distribution for a drug.

The generation of a numerical value for V is explained via Figure 3.11

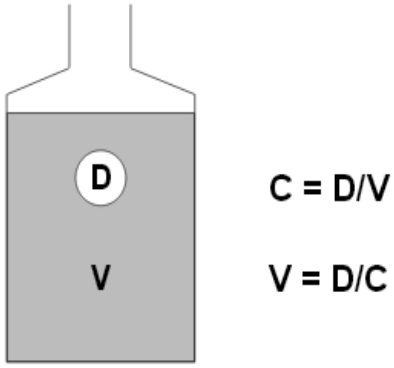

Figure 3.11: The relationship between drug **dose, volume and concentration** for a bottle or a patient.

Start with something simpler than the human body - a bottle. The bottle in Figure 3.11 has a volume of V litres and a dose (D mg) of drug is added and allowed to dissolve and disperse evenly throughout the volume. The resultant concentration (C; in mg/L) will be:

$$C = D/V$$

In an alternative scenario, we might not know the volume of the bottle, but we could determine this by adding a known dose of drug, stirring and then removing a sample for analysis, to determine drug concentration. We then calculate the volume by re-arranging the previous formula:

$$V = D/C$$

We can perform a similar operation in a patient – inject a known dose of drug, remove a blood sample to determine drug concentration and finally obtain a volume by the same calculation. The value we would obtain by this calculation is the volume of distribution for the drug. A simple example is shown in Figure 3.12. It doesn't matter whether the dose (50mg) was delivered into a bottle or a patient or whether the resultant concentration (0.25 mg/L) describes a laboratory solution or a patient's blood sample. Either way the relevant volume is 200 Litres.

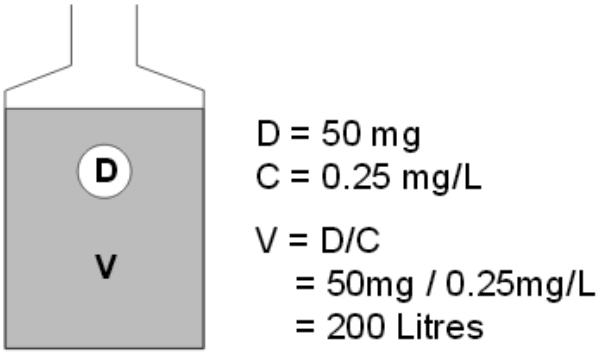

Figure 3.12: A simple example of the relationship between drug dose, concentration and volume for a bottle or a patient

It was stated earlier that the intended physical meaning of the volume of distribution was that it should reflect the extent of drug distribution out of the blood into the tissues.

Figure 3.13 shows that V does indeed reflect that property.

- In (a) most of the drug stays in the blood, leaving a high blood concentration. When we calculate V = D/C

we obtain a small volume. We thus achieve the relationship we wanted – a low tendency for drug to move from the blood into the tissues is associated with a **small value for V**.

- In (b) more of the drug has moved from the blood – this leaves a lower concentration – the calculated value of V is greater.
- In (c) there is very extensive movement – little drug remains in the blood – calculated V is appropriately large, reflecting the degree of movement into the tissues.

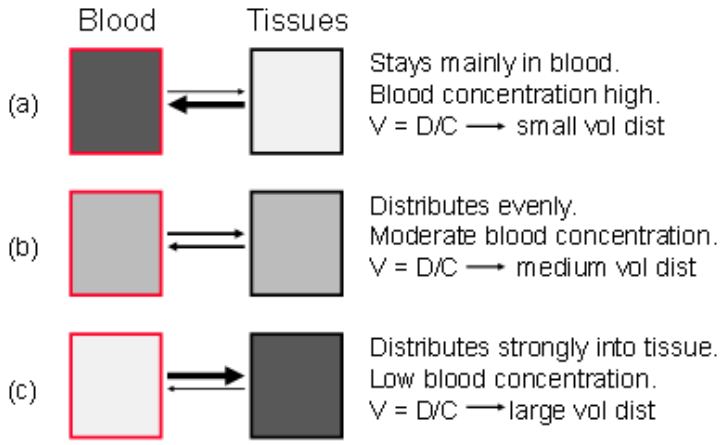

Figure 3.13: The volume of distribution reflects the extent of drug movement out of the blood into tissues

The **three** substances with **small volumes** are retained in the blood for differing reasons. **Adalimumab** is a monoclonal antibody (a protein with a molecular weight well over 100,000) that is virtually restricted to the plasma compartment. **Warfarin** binds tightly to serum albumin which prevents it from distributing and **gentamicin** is a very water soluble antibiotic with limited distribution and very little penetration into cells.

The **three large volume** substances all bind to intracellular components. **Digoxin** binds to a tissue protein, **doxepin** is a very lipid soluble molecule that dissolves into fat in the tissues and **chloroquine** binds strongly to DNA.

Using the volume of distribution to calculate dose size

For clinical purposes, the main use of the volume of distribution is to allow the calculation of a dose of drug that will result in an appropriate blood concentration of drug in a patient. As an example we will calculate a dose size for aminophylline:

The previously recognized relationship:

$C = D / V$

Can be re-arranged to:

$D = C \times V$

Thus, if we know the target concentration for a drug and its likely volume of distribution in a particular patient, we can calculate a suitable dose. The next three sections show the steps in the calculation:

Obtaining a value for the target concentration

For key drugs we know from previous experience that a certain range of blood concentrations is likely to produce an effect that is adequate, but not toxic. With theophylline, we commonly aim for concentrations within the range of 10 to 20 mg/L. We normally target the middle of the acceptable range, so in this case 15 mg/L.

Obtaining a value for the volume of distribution from the population mean expressed on a 'per Kg body weight' basis.

How can we obtain a value for the volume of distribution for a drug in a particular patient, if that patient has not previously been treated with the relevant drug? Fortunately, volume of distribution is closely related to body mass. During the early stages of drug development, the volume of distribution of the drug will be determined in a series of patients. Values will probably vary considerably between patients of differing sizes, but will generally be much more consistent when expressed on a 'per Kg body weight' basis. Thus the actual volume for theophylline in a particular patient might be 35L, but if that patient weighed 70Kg,

this would be reported as 0.5 L/Kg. The generally accepted mean volume for theophylline is 0.48 L/Kg.

The dose calculation

A new patient is to be treated with theophylline (actually administering its salt aminophylline; S = 0.8). He is of fairly normal build and weighs 80Kg. Target concentration for theophylline will be 15mg/L. We would calculate an appropriate intravenous dose of aminophylline in three stages.

- First calculate the patient's likely volume of distribution for theophylline as:

V = 0.48 L/Kg x 80 Kg

= 38.4 L.

- Then calculate a theophylline dose as:

D = C x V

= 15 mg/L x 38.4 L

= 576 mg

- Correct for the salt factor

Dose = D / S

= 576 mg / 0.8

= 720 mg aminophylline

The principle clinical value of the volume of distribution lies in allowing the calculation of a drug dose that will achieve some specified blood concentration.

Predicted volumes, based on body weight, tend to be precise enough for practical purposes, so long as patients are of fairly average build. However, with very over-weight patients, their ratio of fat to muscle will be increased. A relatively water soluble drug like digoxin will show limited distribution into fat and a volume estimated from total body weight is likely to be biased upwards. With such drugs, it is better to estimate volume of distribution from a patient's ideal rather than actual weight.

1000ng = 1μg

1000μg = 1mg

1μg/L = 1ng/mL

1mg/L = 1μg/mL

Practice calculations

1) A drug has a desirable concentration range of 150-250 μg/L. Its mean volume of distribution is 0.72 L/Kg. What bolus i.v. dose should be administered to a patient weighing 65 Kg? (Answer in units of mg).

2) A drug has a mean volume of distribution of 0.91 L/Kg and a desirable concentration range of 20-40μg/L. A 5mg bolus i.v. dose of this drug is to be administered to a patient weighing 80Kg. Is this dose likely to be satisfactory?

3) An initial concentration of 12.5 ng/mL arises following the bolus i.v. administration of 200 μg of a drug. Calculate the volume of distribution of this drug in this patient (in units of L).

4) A dose (5mg) of a salt that contains 70% by weight of the parent drug is administered by bolus i.v. injection. The volume of distribution of the drug is 70 L. Calculate the initial concentration of the drug (in units of ng/mL).

5) 0.5 mg of a drug is administered by bolus i.v. injection. The initial concentration is 20ng/mL. Calculate the volume of distribution of the drug (in units of L).

6) A drug has a mean volume of distribution of 0.45 L/Kg. It is to be administered (bolus i.v. dose) as a salt that contains 75% by weight of the parent drug. The patient weighs 70Kg. The desirable concentration range for the parent drug is 400-700 ng/mL. What dose of the drug should be administered? (Answer in units of mg.