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# Volume of Distribution

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This tutorial deals with basic concepts of volume of distribution, the second most important parameter in pharmacokinetics but often challenging for students in clinical pharmacology. Its relationships with dose, concentration and amount in the body are discussed using a physical model and examples of commonly used drugs, as well as its physiological aspects pertaining to the physical volume of differing organs. Finally, application of volume of distribution to the calculation of loading dose and half-life is used to show how it is essential in pharmacotherapy and clinical pharmacology.

## Principles of Volume of Distribution

The definition of volume of distribution (V, Fig. 1) links drug concentration to the amount of drug in the body.

*Volume of distribution describes the relationship between concentration and the amount of drug in the body*

Figure 1. The definition of volume of distribution

Note it is an *apparent* volume. The apparent volume corresponds to the space that explains the particular concentration given the amount in the whole body. It is an apparent volume because it is defined in terms of a particular concentration.

Because the definition of volume is linked directly to this particular concentration it is important to know in what fluid the concentration is obtained. Most commonly drug volume is based on drug concentration in plasma or serum. For all practical purposes there is no difference between plasma and serum concentrations.

While the apparent volume may be similar to a physical space in the body it is not necessary to assume that the apparent volume corresponds to an anatomical/physiological volume.

If volume is constant then the amount of drug in the body will be linearly proportional to the drug concentration.

$$\text{Amount} = \text{Volume} \cdot \text{Concentration}$$

A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital.[1] It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting.

If the target concentration is known then what loading dose is needed to achieve the target concentration?

The loading dose can be predicted if the target concentration and the drug apparent volume of distribution are known. Note the units of volume are typically L and concentration is mg/L. Loading doses are then readily predicted with units of mg.

$$\begin{aligned} \text{Amount} &= V \cdot \text{Concentration} \\ \text{mg} &= L \cdot \text{mg/L} \\ 350 \text{ mg} &= 35 L \cdot 10 \text{ mg/L} \end{aligned}$$

## The Bathtub Model of Volume of Distribution

The bathtub (Fig. 2) provides a physical model to explain how physical factors can influence the apparent volume.

In this example there is no loss of water from the bathtub.

By putting a known amount of drug (the dose) into the bathtub and measuring the concentration it is easy to calculate the apparent volume.

It is common to distinguish 3 physical volumes based on anatomical and physiological concepts.

Very large molecules (proteins) or blood components (blood cells) will largely be confined to the vascular volume. This vascular volume consists of the total blood volume, the fluid component defined by plasma and the cellular component defined largely by red blood cells.

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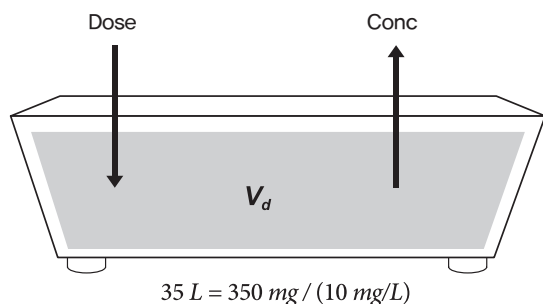


Figure 2. The bathtub model of volume of distribution.

Molecules which can leave the vascular space but do not cross cell membranes easily (e.g. highly ionised molecules) will mainly be in the extracellular compartment.

Molecules which can readily cross cell membranes may share the same physical volume as water.

Typical values are 5 L for blood volume (2.5 L plasma, 2.5 L cells), 18 L for extracellular volume, and 50 L[2,3] for total body water.

Apparent volume of distribution does not necessarily correspond to any physical compartment because of binding to tissues, binding to plasma proteins, preferential partitioning into fat or adsorption onto bone.

An important example of tissue binding is for the drug digoxin. Digoxin binds extensively to  $\text{Na}^+/\text{K}^+$  ATPase. This enzyme is essential for all cells and is found in large quantities in muscle, nervous tissue and the kidneys.

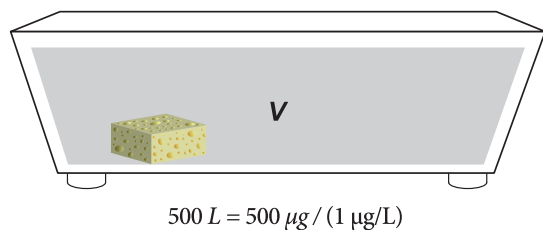


Figure 3. The bathtub with sponge model of volume of distribution.

Binding to tissue receptors that are also the site of action typically contributes only a small amount to the overall tissue distribution of most drugs. It happens that  $\text{Na}^+/\text{K}^+$  ATPase is also the site of action of digoxin therefore digoxin is unusual in this regard.

The binding of digoxin to  $\text{Na}^+/\text{K}^+$  ATPase is analogous to a drug being put in a bathtub and binding to a sponge in the water (Fig. 3). When drug concentration is measured in the water, it will be lower than it would have been if it was uniformly distributed in the tub (e.g. 1  $\mu\text{g}/\text{L}$ ). Because the measured con-

centration is lower, the apparent volume must be larger than the physical volume.

The apparent volume of distribution will be large when there is extensive binding to tissue proteins.

Some drugs may have a large apparent volumes because of partitioning rather than binding to tissues.

Partitioning into fat can make the apparent volume of distribution larger in obese people.

Some drugs adsorb to bone e.g. tetracycline and bisphosphonates. Tetracycline causes teeth staining in children. Bisphosphonate adsorption can be beneficial in osteoporosis by reducing bone breakdown. Some poisonous substances e.g. radioactive caesium, are adsorbed to bone and can cause bone cancer. All these substances will have relatively large volumes of distribution.

Plasma protein binding is another major reason why the apparent volume of distribution does not correspond to a physical volume. But binding to plasma will lead to a smaller apparent volume. Drugs bind to proteins like albumin and  $\alpha_1$ -acid-glycoprotein. Because they bind to plasma proteins they are extracted from plasma and included in drug concentration measurements. This gives a misleading impression of the volume of distribution and this phenomenon can be thought of as a 'red herring'[4]

Imagine there are 'red herrings' swimming in the bathwater (Fig. 4). When a sample of bathwater is removed it also takes 'red herrings' with it. The concentration of drug will be higher in the sample than in the rest of the bath water because of the higher concentration of drug bound to the 'red herrings'. The 'red herring' effect is caused by drug binding to plasma proteins. A higher concentration in the sample leads to a lower apparent volume of distribution.

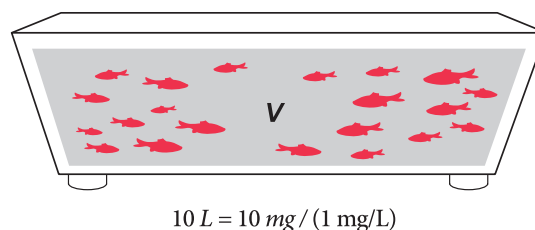


Figure 4. The bathtub with red herring model of volume of distribution.

### Total and Unbound Plasma Concentration

Warfarin is extensively bound to plasma proteins. About 99% of warfarin in plasma is bound to albumin leaving only 1% unbound. Based on total warfarin concentration the apparent volume of distribution is 10 L. But based on unbound concentration it is 1000 L.

### Plasma Concentrations of Warfarin

Total	=	1 mg/L
Bound	=	0.99 mg/L
Unbound	=	0.01 mg/L

### Apparent Volume

Total	= 10 mg/1 mg/L	= 10 L
Unbound	= 10 mg/0.01 mg/L	= 1000 L

Which is the correct apparent volume 10 L or 1000 L?

Both values are correct !

The apparent volume will vary according to whether total or unbound drug is used for the calculation. The ideal way to measure drug concentration is in the unbound form but this method is technically demanding, less precise and often a lot more expensive. If the plasma protein binding fraction remains constant then it does not matter if total or unbound concentrations are used. The loading dose calculated from the apparent volume will be the same as long as the target concentration type (total or unbound) matches with the apparent volume type (total or unbound).

Based on total drug concentration the apparent volume of distribution will be small when there is extensive binding to plasma proteins.

### Plasma Protein Binding Displacement

Understanding how drugs like warfarin (fraction unbound  $f_u = 0.01$ ) bind to plasma proteins can help understand what happens if a drug (e.g., naproxen) that also binds to plasma proteins and can displace warfarin from its plasma protein binding site is given.

Plasma proteins make a small contribution to bound amount in body. Plasma (2.5 L) is approximately 25% of warfarin volume of distribution (10 L). A published example with naproxen displaced only 0.1%.

In an extreme case, imagine that 10% of warfarin in plasma is displaced by a displacing drug.

This will lead to only a 2.5% increase in unbound amount in the body (sum of unbound warfarin in central and peripheral compartments) which occurs rapidly at the time the displacing drug is given.

This 2.5% increase in unbound drug will have a negligible acute effect on total unbound amount in body and an undetectable effect on warfarin anti-coagulant effect (5, 6).

If the unbound clearance of warfarin is unaffected by the displacing drug and the drug dose rate (rate in) remains unchanged then no steady state change in concentration will occur. Therefore there will be no change in warfarin anti-coagulant effect.

### Physiological Basis of Volume of Distribution

**Tiny:** Warfarin 10 L; Less than Extra Cellular Fluid (ECF), Greater than Blood, Plasma protein binding

Warfarin has a very small apparent volume (based on total concentration) because it binds extensively to plasma proteins. It has a big red herring effect. The apparent volume is less than extracellular fluid but larger than plasma volume – an impossible situation for a physical volume of distribution.

**Small:** Gentamicin 18 L; Approximately the same as ECF

Gentamicin does not bind to plasma proteins. It is highly ionised and does not cross cell membranes easily. Its apparent volume of distribution is quite close to the physical volume of extracellular fluid (ECF). This indicates that it does not bind extensively to tissues.

**Medium:** Theophylline 35 L; Total Body Water

Theophylline has a medium size apparent volume of distribution. It is not particularly polar so is expected to cross cell membranes. Its apparent volume of distribution is close to total body water. Because it does not bind to plasma proteins this suggests it does not bind extensively to tissues either.

**Large:** Digoxin 500 L;  $\text{Na}^+/\text{K}^+$  ATPase binding; Muscle, kidney, nervous tissue

Digoxin has a very large apparent volume of distribution—several times bigger than the typical human physical volume of 70 L. It has negligible binding to plasma proteins but high affinity and extensive binding to tissues containing  $\text{Na}^+/\text{K}^+$  ATPase.

### Time Course of Distribution

When the time course of drug distribution is considered it is possible to conceptualize a compartment defined by a time dependent apparent volume of distribution. Initially a drug is distributed in the plasma volume (initial volume of distribution) then diffuses into the extracellular space then into cells. Mixing in the plasma fluid and diffusion to tissue fluids takes time and the apparent volume of distribution changes with time. At steady state the volume no longer increases with time (steady state volume of distribution).

For simplicity it is common to consider one or more pharmacokinetic compartments representing drug distribution at some point in time. The central compartment reflects the initial rapid distribution space while the tissue compartment reflects the space after sufficient time has passed to reach a steady state of distribution.

Apparent central compartment volume is approximately ECF volume. Apparent tissue compartment volume depends on tissue binding and partition.

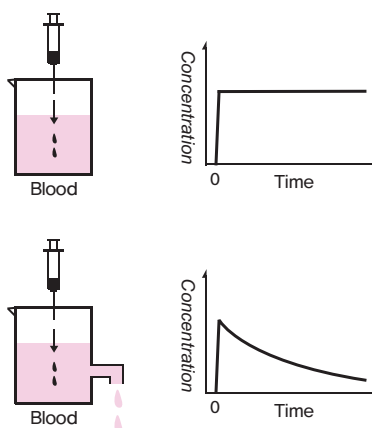


Figure 5. The one compartment model of distribution.

Figure 5 illustrates an example of a one compartment system.

In the lower beaker it is necessary to imagine fluid (without drug) is entering at the same rate as fluid is lost so that the volume of the beaker remains constant.

The upper beaker is injected with a dose of drug and the concentration stays constant because there is no elimination. The lower beaker is losing fluid so drug concentration declines. The initial volume of distribution is identical in both cases so the initial concentration is the same.

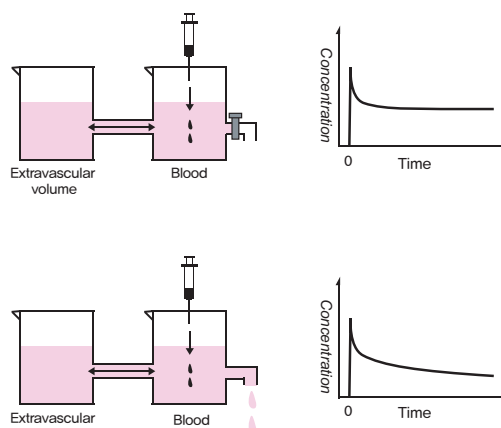


Figure 6. The two compartment model of distribution.

If a second beaker is connected to the first (Fig. 6) we have a two compartment system. Without elimination of fluid we can see the same initial volume of distribution determined by the first beaker. But as time passes and drug distributes to and back from the second beaker a new apparent 'steady state' volume is reached. This is larger than the initial volume. The concept is easily seen when no elimination takes place from the system. When elimination

occurs as well there is still a steady state apparent volume defined by the sum of the volumes in both beakers but the concentration falls continuously.

In the lower beaker it is necessary to imagine fluid (without drug) entering at the same rate as fluid is lost so that the volume of the beaker remains constant.

The time course of distribution of drug to tissues varies widely among drugs. Some drugs like thiopental (an intravenously administered short acting anaesthetic) distribute rapidly to the brain then to the rest of the tissues of the body. It is re-distribution of thiopental to the rest of the body that leads to loss of effect.

Digoxin binds extensively to tissue receptors ( $\text{Na}^+/\text{K}^+$  ATPase). This binding process is quite slow and it takes hours to reach a binding equilibrium. The apparent volume of distribution takes a long time to reach its steady state value.

Lithium is like sodium and exchanges slowly for sodium inside cells. This re-distribution process can take days which explains why it takes a long time for lithium to reach a steady state volume.

### Clinical Application

The main clinical application of understanding about volume of distribution is for prediction of the loading dose to achieve a target concentration.

$$\text{Loading Dose} = V \times \text{Target Concentration}$$

A second useful application is the ability to calculate the half-life. This requires the clearance (CL) to be known as well as the apparent volume of distribution (V).

$$T_{1/2} = \frac{0.7 \times V}{CL}$$

### Conflict of interest

The authors have no conflict of interest.

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