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Volume of Distribution

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Objectives

- Learn the definition of volume of distribution
- Understand the physiological determinants of volume of distribution
- Realize the limited relevance of plasma protein binding
- Be able to describe the time course of drug concentration for one and two compartment pharmacokinetic models
- Appreciate the applications of volume concepts to clinical practice

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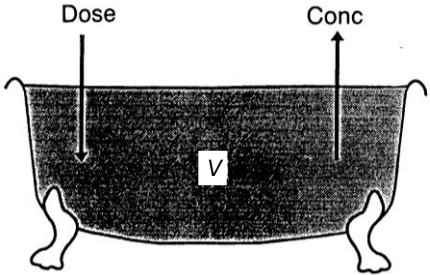
Volume of Distribution

Apparent Volume of Distribution describes the relationship between concentration and the amount of drug in the body

$$\text{Amount} = V \bullet \text{Conc}$$

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The definition of apparent volume of distribution (V) links drug concentration to the amount of drug in the body. Note it is an *apparent* volume. While the 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.

<p>Slide 4</p>	<h2 style="text-align: center; color: red;">Theophylline Target Concentration</h2> <p style="text-align: center;">Clin. Pharmacokinet. 25 (6): 495-505, 1993</p> <p style="text-align: center;">Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial</p> <p style="text-align: center;"><i>Nicholas Holford¹, Peter Black¹, Ron Couchl², Julia Kennedy³ and Robin Briant¹</i></p> <p style="text-align: center;">1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand</p> <p>➤ How can a target concentration of 10 mg/L be achieved?</p> <p style="font-size: small; text-align: center;">©NHG Holford, 2021, all rights reserved.</p>	<p>A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. 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 what dose rate is needed to achieve the target concentration?</p>
<p>Slide 5</p>	<h2 style="text-align: center; color: red;">Loading Dose</h2> $\text{Amount} = V \bullet \text{Conc}$ $\text{mg} = \text{L} \bullet \text{mg/L}$ $350 \text{ mg} = 35 \text{ L} \bullet 10 \text{ mg/L}$ <p style="font-size: small; text-align: center;">©NHG Holford, 2021, all rights reserved.</p>	<p>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.</p>
<p>Slide 6</p>	<h2 style="text-align: center; color: red;">Bathtub Model</h2>  $V = \frac{\text{Amount}}{\text{Conc}} \quad 35\text{L} = \frac{350\text{mg}}{10\text{mg/L}}$ <p style="font-size: small; text-align: center;">©NHG Holford, 2021, all rights reserved.</p>	<p>The bathtub 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.</p>

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Physical Compartments

- Physiological
 - » Vascular
 - Blood = 5 L
 - Plasma = 2.5 L
 - » Extracellular
 - 18 L (0.25 L/kg)
 - » Total Body Water
 - 35 L (0.5 L/kg)

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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.

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 volume.

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

Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females estimated from simple anthropometric measurements. *The American Journal of Clinical Nutrition*. 1980;33(1):27-39.
Chumlea W, Guo S, Zeller C, Reo N, Baumgartner R, Garry P, et al. Total body water reference values and prediction equations for adults. *Kidney Int*. 2001;59:2250 - 8.

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Tissue Binding

- Tissue Proteins
 - » Na⁺ K⁺ ATPase binding
 - Large contribution for digoxin
 - » Other drug receptors
 - Usually small contribution

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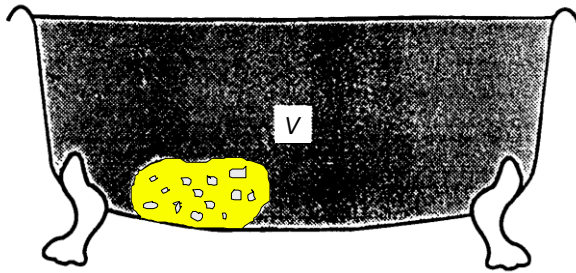
Apparent volume of distribution does not necessarily correspond to any physical compartment because of binding to tissues, binding to plasma proteins, preferential partitioning into fat or adsorption onto bone.

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

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 Na⁺K⁺ATPase is also the site of action of digoxin therefore digoxin is unusual in this regard.

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Sponge Model



$$V = \frac{\text{Amount}}{\text{Conc}} \quad 350L = \frac{350\text{mg}}{1\text{mg/L}}$$

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The binding of digoxin to Na+K+ATPase is analogous to a drug being put in a bathtub and binding to a sponge in the water. 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. Because the measured concentration 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.

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Partition

- Fat
 - » Lipophilic drugs - Increased V
 - thiopentone
 - » Hydrophilic drugs - No effect on V
 - digoxin
- Bone
 - » Adsorption
 - tetracycline, bisphosphonates, [radioactive caesium]

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Some drugs have 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.

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Plasma Protein Binding

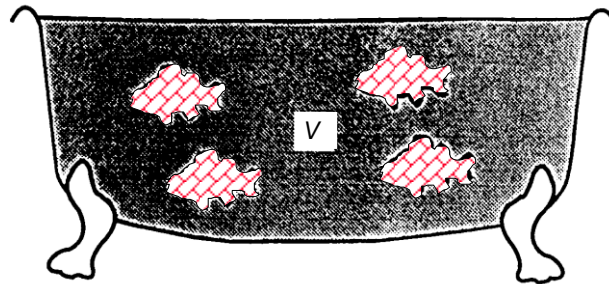
- Plasma Proteins
 - » Albumin
 - mainly weak acids e.g. warfarin
 - » Alpha₁-acid-glycoprotein
 - mainly weak bases e.g. lignocaine
 - » “Red Herring”

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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 alpha₁-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’ (<http://www.nizkor.org/features/fallacies/red-herring.html>).

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Red Herring Model



$$V = \frac{\text{Amount}}{\text{Conc}} \quad 3.5L = \frac{350\text{mg}}{100\text{mg/L}}$$

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Imagine there are red herrings swimming in the bathwater. 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.

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

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Red Herrings and Volume

➤ 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

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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.

Which is the correct apparent volume?

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).

<p>Slide 14</p>	<h2 style="text-align: center;">Binding</h2> <ul style="list-style-type: none"> ➤ Plasma Proteins <ul style="list-style-type: none"> » Small contribution to bound amount in body » Plasma is approx 25% of warfarin volume <ul style="list-style-type: none"> – 10% of this may be displaced e.g by ibuprofen – Only 2.5% increase in unbound amount » Negligible acute effect on total unbound amount in body » No steady state change in concentration or effect if unbound drug clearance is unaffected and drug dose rate (rate in) is unchanged <p><small>©NEIG Hofford, 2021, all rights reserved.</small></p>	<p>Because plasma proteins are only a small part of the tissues that bound drug in the body there is a negligible effect on unbound drug concentration if plasma protein binding is changed e.g. by displacement with a competing drug.</p>
<p>Slide 15</p>	<h2 style="text-align: center;">Apparent Volume of Distribution Physiological Basis</h2> <ul style="list-style-type: none"> ➤ Tiny <ul style="list-style-type: none"> » Warfarin 10 L <ul style="list-style-type: none"> – Less than ECF, Greater than Blood – Plasma protein binding ➤ Small <ul style="list-style-type: none"> » Gentamicin 18 L <ul style="list-style-type: none"> – Approx. ECF <p><small>©NEIG Hofford, 2021, all rights reserved.</small></p>	<p>ECF = Extra Cellular Fluid 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. 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.</p>
<p>Slide 16</p>	<h2 style="text-align: center;">Apparent Volume of Distribution Physiological Basis</h2> <ul style="list-style-type: none"> ➤ Medium <ul style="list-style-type: none"> » Theophylline 35 L <ul style="list-style-type: none"> – Total Body Water ➤ Large <ul style="list-style-type: none"> » Digoxin 500 L <ul style="list-style-type: none"> – Na⁺ K⁺ ATPase binding – Muscle, kidney, nervous tissue <p><small>©NEIG Hofford, 2021, all rights reserved.</small></p>	<p>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.</p> <p>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 Na⁺K⁺ATPase.</p>

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Pharmacokinetic Compartments

- Apparent Central Compartment Volume
 - » Approximately Extracellular Fluid volume
- Apparent Tissue Compartment Volume
 - » Depends on Tissue Binding and Partition

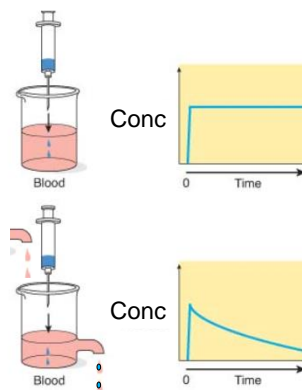
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When the time course of drug distribution is considered it is possible to conceptualize a compartment defined by a time dependent apparent volume of distribution. Initially a drug is distributed in the plasma volume (initial volume of distribution) 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.

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One Compartment Model



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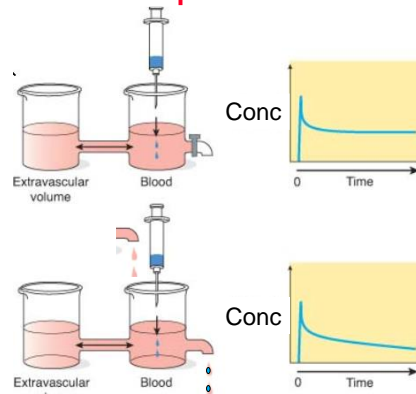
This figure illustrates an example of a one compartment system. In the lower beaker there is fluid (without drug) entering at the same rate as fluid is lost so that the volume of the beaker remains constant.

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 adapted from: Holford NHG. Pharmacokinetics and pharmacodynamics: Rational dose selection & the time course of drug action. In: Katzung B, Masters SB, Trevor AJ editors. Basic and Clinical Pharmacology. 13 ed. San Francisco: McGraw-Hill Medical; 2014.

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Two Compartment Model



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If a second beaker is connected to the first 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 there is fluid (without drug) entering at the same rate as fluid is lost so that the volume of the beaker remains constant.

Figure adapted from: Holford NHG. Pharmacokinetics and pharmacodynamics: Rational dose selection & the time course of drug action. In: Katzung B, Masters SB, Trevor AJ editors. Basic and Clinical Pharmacology. 13 ed. San Francisco: McGraw-Hill Medical; 2014.

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Distribution Rate

- Distribution Half-Life
 - » Minutes
 - Thiopentone
 - » Hours
 - Digoxin
 - » Days
 - Lithium

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The time course of distribution of drug to tissues varies widely among drugs. Some drugs like thiopentone (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 thiopentone to the rest of the body that leads to loss of effect. Digoxin binds extensively to tissue receptors (Na+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.

Applications

➤ Loading Dose

$$\text{Loading Dose} = V \cdot \text{Target Conc}$$

➤ Half-Life

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

The main clinical application of understanding about volume of distribution is for prediction of the loading dose.

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).