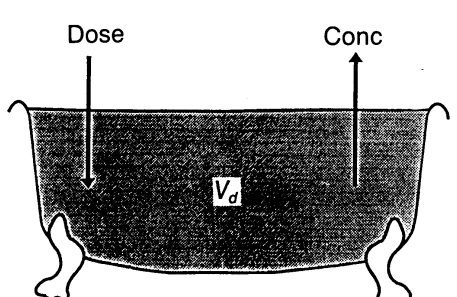


<p>Slide 1</p>	<h2 style="text-align: center;">Volume of Distribution</h2> <p style="text-align: center;">Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand</p>	
<p>Slide 2</p>	<h2 style="text-align: center;">Objectives</h2> <ul style="list-style-type: none"> ● 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 <p><small>©NHG Holford, 2011, all rights reserved.</small></p>	
<p>Slide 3</p>	<h2 style="text-align: center;">Volume of Distribution</h2> <p style="text-align: center;"><i>Apparent Volume of Distribution describes the relationship between <u>concentration</u> and the <u>amount</u> of drug in the body</i></p> $\textit{Amount} = V \bullet \textit{Conc}$ <p><small>©NHG Holford, 2011, all rights reserved.</small></p>	<p>The definition of apparent volume of distribution (V) links drug concentration to the amount of drug in the body. Note it is an <i>apparent</i> 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>

<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 Couch², 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> <ul style="list-style-type: none"> ● How can a target concentration of 10 mg/L be achieved? <p style="font-size: small; text-align: center;">©NHG Holford, 2011, 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.</p> <p>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, 2011, all rights reserved.</p>	<p>The loading dose can be predicted if the target concentration and the drug apparent volume of distribution are known.</p> <p>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, 2011, all rights reserved.</p>	<p>The bathtub provides a physical model to explain how physical factors can influence the apparent volume.</p> <p>In this example there is no loss of water from the bathtub.</p> <p>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 compartment. This space can be divided into the total blood volume and the fluid component defined by plasma. 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 will share the same apparent volume as water.

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Binding

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

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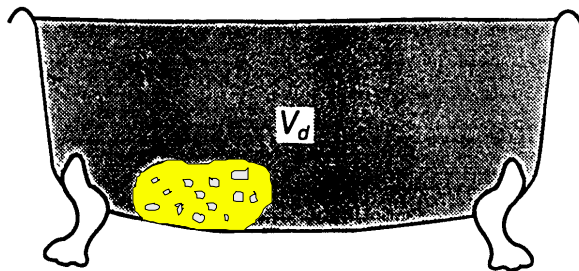
Apparent volume of distribution does not necessarily correspond to any physical compartment because of binding to tissues, binding to plasma proteins or partitioning into fat or adsorption onto bone.

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. It happens that Na⁺K⁺ATPase is also the site of action of digoxin.

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.

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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.

Slide 10

Binding

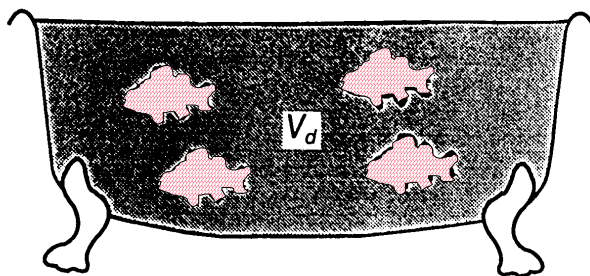
- Plasma Proteins
 - » Albumin
 - mainly weak acids e.g. warfarin
 - » Alpha₁-acid-glycoprotein
 - mainly weak bases e.g. lignocaine
 - » “Red Herring”

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Plasma protein binding is another major reason why the apparent volume of distribution does not correspond to a physical volume. Drugs bind to proteins like albumin and alpha1-acid-glycoprotein. Because they bind to plasma proteins they are extracted from plasma when drug concentrations are measured. 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.

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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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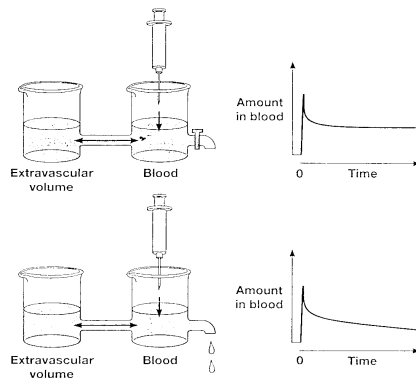
Warfarin is extensively bound to plasma proteins. About 99% of warfarin in plasma is bound to albumin leaving only 1% unbound. Based on total warfarin concentration the apparent volume of distribution is 10 L. But based on unbound concentration it is 1000 L. Which is the correct apparent volume? Both values are correct! The apparent volume will vary according to whether total or unbound drug is measured. The ideal way to measure drug concentration is in the unbound form but this 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 13</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 – Only 2.5% increase in unbound amount » Negligible acute effect on total unbound amount in body » No steady state effect because unbound drug clearance is unchanged <p><small>©NHG Hallford, 2011, 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 14</p>	<h2 style="text-align: center;">Partition</h2> <ul style="list-style-type: none"> ● Fat <ul style="list-style-type: none"> » Lipophilic drugs - Increased V <ul style="list-style-type: none"> – thiopentone » Hydrophilic drugs - No effect on V <ul style="list-style-type: none"> – digoxin ● Bone <ul style="list-style-type: none"> » Adsorption <ul style="list-style-type: none"> – tetracycline, bisphosphonates, [radioactive Caesium] <p><small>©NHG Hallford, 2011, all rights reserved.</small></p>	<p>Some drugs have large apparent volumes because of partitioning rather than binding. 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.</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>©NHG Hallford, 2011, all rights reserved.</small></p>	<p>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. It's 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; color: red;">Apparent Volume of Distribution Physiological Basis</h2> <ul style="list-style-type: none"> ● Medium <ul style="list-style-type: none"> » Theophylline 35 L – Total Body Water ● Large <ul style="list-style-type: none"> » Digoxin 500 L – Na⁺ K⁺ ATPase binding – Muscle, kidney, nervous tissue <p style="font-size: small; margin-top: 10px;">©NHG Holford, 2011, all rights reserved.</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>Slide 17</p>	<h2 style="text-align: center; color: red;">Pharmacokinetic Compartments</h2> <ul style="list-style-type: none"> ● Apparent Central Compartment Volume <ul style="list-style-type: none"> » Approximately Extracellular Fluid volume ● Apparent Tissue Compartment Volume <ul style="list-style-type: none"> » Depends on Tissue Partition and Binding <p style="font-size: small; margin-top: 10px;">©NHG Holford, 2011, all rights reserved.</p>	<p>When the time course of drug distribution is considered it is possible to conceptualize another kind of compartment defined by a time dependent apparent volume of distribution. Initially a drug is distributed in the plasma volume 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.</p> <p>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.</p>
<p>Slide 18</p>	<h2 style="text-align: center; color: red;">One Compartment Model</h2> <div style="text-align: center;"> </div> <p style="font-size: small; margin-top: 10px;">©NHG Holford, 2011, all rights reserved.</p>	<p>This figure illustrates an example of a one compartment system. 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.</p> <p>Figure adapted from: Holford NHG. Pharmacokinetics and pharmacodynamics: Rational dose selection & the time course of drug action. In: Katzung BM, S.B., Trever AJ, editors. Basic and Clinical Pharmacology. 11 ed. San Francisco: McGraw-Hill Medical; 2009. p. 37-51.</p>

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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.

Figure adapted from: Holford NHG. Pharmacokinetics and pharmacodynamics: Rational dose selection & the time course of drug action. In: Katzung BM, S.B., Trever AJ, editors. Basic and Clinical Pharmacology. 11 ed. San Francisco: McGraw-Hill Medical; 2009. p. 37-51.

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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 exchange 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

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

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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).