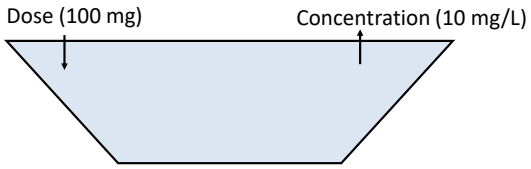
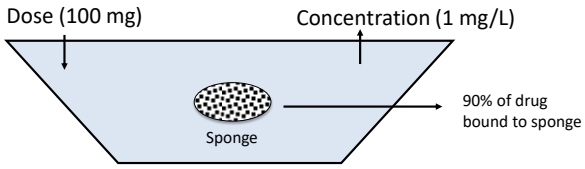
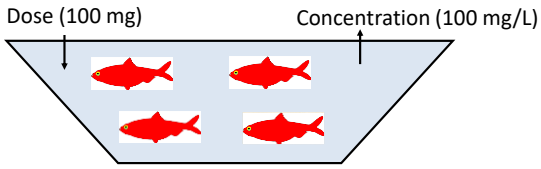
Slide 1	# Volume of Distribution MBChB 221B Dr Stephen Jamieson Dept of Pharmacology and Clinical Pharmacology Auckland Cancer Society Research Centre	
Slide 2	## Learning objectives • Learn the definition of volume of distribution • Understand the physiological determinants of volume of distribution • Realise 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	
Slide 3	## Drug distribution • The reversible movement of drug between body compartments once it has entered the systemic circulation • Influenced by physicochemical properties of drugs – Size – Ionisation – Lipophilicity – Plasma protein binding • Defined by the parameter known as volume of distribution (V)	Drug distribution is the transfer of drug from the systemic circulation to various body compartments or tissues. Most drugs act outside the systemic circulation so need to first distribute to the site of action to have their effect. In order to exit out of blood vessels and widely distribute throughout the body, drugs need to be small, non-ionised, lipophilic and unbound to plasma proteins so that they can cross cell membranes. Volume of distribution or V is the key pharmacokinetic parameter that describes the process of drug distribution.

Slide 4	**Volume of distribution (V)** $V = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$ • Determined by: – Body mass and composition – Tissue blood flow – Tissue binding (↑V) – Plasma protein binding (↓V) – Physico-chemical properties of the drug • (e.g. size, lipophilicity, ionisation) – Natural barriers (e.g. blood brain barrier)	The definition of apparent volume of distribution 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 a physiological volume. There are multiple factors that determine drug distribution. Larger people have greater space for the drug to distribute and can have a larger V. Delivery of drug to tissues is determined by tissue blood flow. Binding of drugs in tissues or plasma influences the amount of drug in the body relative to the plasma and alters V. Physico-chemical properties influence the ability of the drug to diffuse across membranes and distribute throughout the body. Natural barriers can limit drug distribution and reduce V.
Slide 5	**Bathtub model of V**  V = amount/concentration = 100 mg / 10 mg/L = 10 L	The bathtub analogy can also be used to describe V. 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.
Slide 6	**Apparent volume of distribution (V)** • The volume that the drug must be dissolved in to give a concentration equivalent to that found in plasma – Gives an indication of distribution out of plasma into tissues – $V = \text{amount}/\text{conc}_{plasma}$ • Not a physiological value • Total body water in 70 kg person ≈ 42 L – Blood volume ≈ 5L, plasma ≈ 3L – Extracellular volume ≈ 14L – Intracellular volume ≈ 28L – V can exceed 42L (e.g. chloroquine is >10000L) • Drug that rapidly distributes to tissues will have high V • Drug that stays in plasma will have low V	It is common to distinguish 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 as they are too large to exit out of blood vessels. 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 are ionised or hydrophilic and do not cross cell membranes easily will mainly distribute throughout the extracellular volume (plasma and interstitial fluid). Molecules which can readily cross cell membranes may share the same physical volume as water. Some drugs that are found in much higher concentrations in tissues

		than plasma can have a very high V that far exceeds total body water.
Slide 7	**Apparent volume of distribution (V)** • Reasons why V is not physiological – Binding to tissues • Have high V • e.g. Digoxin binds to Na^+/K^+ ATPase – Binding to plasma proteins – Partitioning into tissues	Apparent volume of distribution does not necessarily correspond to any physical compartment because of binding to tissues, binding to plasma proteins and partitioning into tissues. An important example of tissue binding is for the drug digoxin. Digoxin binds extensively to the Na^+/K^+ ATPase, which is essential for all cells and found throughout the tissues. Binding to tissue receptors typically contributes only a small amount to the overall tissue distribution of most drugs. Digoxin is unusual in this regard as the Na^+/K^+ ATPase is also the site of action of digoxin.
Slide 8	**Sponge model of V**  V = amount/concentration = 100 mg / 1 mg/L = 100 L	The binding of digoxin to the Na^+/K^+ ATPase is analogous to a drug being put in a bathtub and binding to a sponge in the water. When the 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.
Slide 9	**Apparent volume of distribution (V)** • Reasons why V is not physiological – Binding to tissues – Binding to plasma proteins • V is misleading (“red herring”) – Bound drug is pharmacologically inactive • e.g. warfarin to albumin, imatinib to $alpha_1$-acid-glycoprotein – Partitioning into tissues	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 have the opposite effect of tissue binding and 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’.

Slide 10	**Red Herring Model**  V = dose/concentration = 100 mg / 100 mg/L = 1 L	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.
Slide 11	**V of plasma protein bound drugs** • Many drugs are highly plasma protein bound – e.g. warfarin 99% bound to albumin • Plasma concentrations of warfarin – Total = 1 mg/L – Bound = 0.99 mg/L – Unbound = 0.01 mg/L • Apparent V for a 10 mg dose of warfarin – Total = 10 mg / 1 mg/L = 10 L – Unbound = 10 mg / 0.01 mg/L = 1000 L	Warfarin is about 99% bound to albumin with only 1% unbound. Based on total warfarin concentrations the apparent volume of distribution is 10 L. But based on unbound concentrations it is 1000 L. 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 since this is the active form of the drug but this method is technically demanding, less precise and often a lot more expensive, so total drug concentrations are generally used. The plasma protein binding fraction usually remains constant, in which case it does not matter if total or unbound concentrations are used.
Slide 12	**Clinical relevance of plasma protein binding** • Approx 50% of drugs are >90% bound to plasma proteins – Unbound drug concentrations are responsible for effect • Impact of alteration of plasma protein binding – e.g. by displacement with competing drug or through disease – Increased elimination of unbound drug – No change in steady state unbound drug concentration • Only in rare cases can reduction in plasma protein binding due to disease or drug interactions alter clinical response – Rapidly cleared IV drugs that are highly plasma protein bound with a narrow therapeutic index	Many clinically-used drugs are highly bound to plasma proteins. The bound drug remains in the systemic circulation and is pharmacologically inactive, yet there is still sufficient free drug available for the drug to be effective. What happens to these drugs if plasma protein binding is released and more drug becomes available? Is clinical response altered? Only in very rare situations (rapidly cleared IV drugs with a narrow therapeutic index). For most drugs, following displacement from plasma proteins, the extra free drug will be eliminated and there will be no change in the steady state unbound drug concentration and no change in clinical response, although total drug concentrations will be reduced.

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Apparent volume of distribution (V)

- Reasons why V is not physiological
  - Binding to tissues
  - Binding to plasma proteins
  - Partitioning into tissues
    - Lipophilic drugs into fat
      - e.g. chloroquine
      - May lead to dosing problems in obese patients where fat content is much higher
    - Drug adsorption onto bone
      - e.g. bisphosphonates (alendronic acid)

Another reason why some drugs have large apparent volumes is because of partitioning rather than binding to tissues, such as partitioning into fat or adsorption onto bone.
Partitioning into fat can make the apparent volume of distribution larger in obese people.

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Physiological Basis of V: examples

- Warfarin: V ≈ 10 L
  - Less than extracellular fluid, larger than plasma volume
  - Highly plasma protein bound
- Gentamicin: V ≈ 16 L
  - Similar to extracellular fluid
  - Highly ionised, low 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.

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. This indicates that it does not bind extensively to tissues.

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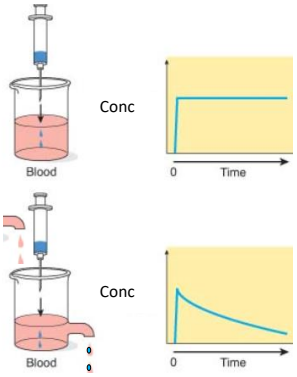
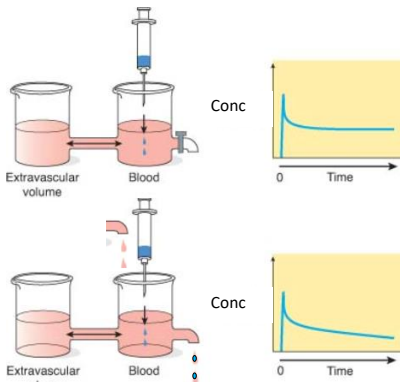
Physiological Basis of V: examples

- Theophylline: V ≈ 35 L
  - Similar to total body water
  - Non-polar, low plasma protein binding
- Digoxin: V ≈ 500 L
  - Na^+/K^+ ATPase binding
  - Muscle, kidney, nervous tissue

Theophylline is non-polar so is expected to cross cell membranes. Its apparent volume of distribution is close to total body water, which we would expect based on its physico-chemical properties, suggesting that it does not bind extensively to tissues.

Digoxin has a very large apparent volume of distribution. It has negligible binding to plasma proteins but high affinity and extensive binding to tissues containing the Na^+/K^+ ATPase.

Slide 16	**Pharmacokinetic compartments** • Apparent central compartment volume – Instantaneous distribution • Apparent tissue compartment volume – Delayed distribution – Depends on tissue binding and partition	When the time course of drug distribution is considered it is possible to conceptualise a compartment defined by a time-dependent apparent volume of distribution. Initially a drug distributes throughout the plasma then diffuses out into the extracellular space and then into the cells. This process takes time and so the apparent volume of distribution will change with time. A steady state volume of distribution will occur when the volume no longer changes with time. 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.
Slide 17	**One compartment model**  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.	A one compartment model can be used to explain instantaneous distribution. This may refer to just the plasma if the drug only instantaneously distributes through the plasma, but it may also refer to the whole body if the drug instantaneously distributes through the whole body. In the top beaker, the beaker is injected with a dose of drug and the concentration stays constant because there is no elimination. In the bottom beaker, the drug is being eliminated, but there is fluid (without drug) entering at the same rate as fluid is lost so that the volume of the beaker remains constant. Note: that in both cases, distribution is instantaneous and so the initial volume of distribution (and the initial concentration) is identical and that in this example elimination is a first-order process. .

Slide 18	**Two compartment model**  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.	We can join the central compartment to a peripheral compartment for a two compartment model. Note: the initial volume of distribution and initial concentration that is achieved here is the same as with the one compartment model, reflecting that the drug instantaneously distributes in the first ("blood") beaker. Over time, the drug can then distribute to the second ("extravascular volume") beaker and a new steady state volume is reached. This volume will be larger than the initial volume, indicating that the drug has distributed into a larger volume. 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 over time.
Slide 19	**Importance of V** • Can be used to calculate loading dose (LD) • V influences – Time to reach steady-state – Time for all the drug to be eliminated • V does not influence the steady state conc (C_{ss}) • C_{ss} is determined by – Clearance of the drug – Rate of input	The main use of V is to calculate a loading dose to ensure that target concentrations are reached quickly. V can help calculate a loading dose because it influences the time taken to reach steady state. The more the drug has distributed the longer it will take to reach steady-state. It will also take longer to be eliminated, because the drug has to redistribute back into the plasma before it can be eliminated. V influences time to steady state, but not steady state concentrations. Steady state concentrations are determined by clearance and the rate of input.
Slide 20	**Loading dose (LD)** • Initial dose administered to achieve a target concentration rapidly – Dependent on V – Helps to fill bath (V) faster to rapidly achieve the target concentration – The bigger the V the higher the dose required to achieve target concentration **Loading dose (mg) = V (L) x target concentration (mg/L)** • If no loading dose is used, the volume takes time to fill up, so the larger the V the longer the time to reach the target conc • Usually given as IV bolus so that target conc is reached quickly, then maintained by IV infusion, but oral loading doses can also be used	To achieve a target concentration in the plasma rapidly, we need to account for the drug that has distributed out of the plasma. V must be filled before the target concentration is reached, therefore we can calculate the loading dose as V x target concentration. A loading dose ensures the target concentrations are achieved quickly and can then be maintained through a maintenance dose. A loading dose is typically a single IV bolus dose or oral dose in units of mg, rather than mg/h (maintenance dose).

Slide 21	## Loading dose calculation • What is the loading dose of theophylline for a patient with asthma to achieve a target concentration of 10 mg/L? – V of theophylline = 35L – Loading dose = 10 mg/L x 35 L = 350 mg • Maintenance dose was 28 mg/h – CL (L/h) x target conc (mg/L)	
Slide 22	## Revision questions • Describe the physiochemical properties of theophylline that influence its distribution • Explain why apparent volume of distribution is not a physiological value, using a drug example • Describe the impact of plasma protein binding on the clinical activity of warfarin	