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_D)

Slide 4

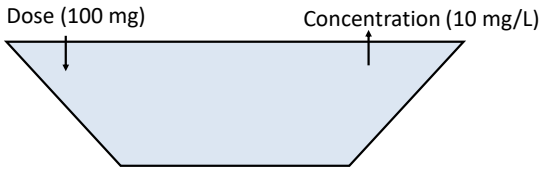
Volume of distribution (V_D)

$$V_D = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

- Determined by:
  - Body mass and composition
  - Tissue blood flow
  - Tissue binding ($\uparrow V_D$)
  - Plasma protein binding ($\downarrow V_D$)
  - Physico-chemical properties of the drug
    - (e.g. size, lipophilicity, ionisation)
  - Natural barriers (e.g. blood brain barrier)

Slide 5

Bathtub model of V_D



V_D = amount/concentration = 100 mg / 10 mg/L = 10 L

Slide 6

Apparent volume of distribution (V_D)

- 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
  - $V_D = \text{amount}/\text{conc}_{plasma}$
- 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_D can exceed 42L (e.g. V_D of quinacrine is 38000L)
- Drug that rapidly distributes to tissues will have high V_D
- Drug that stays in plasma will have low V_D

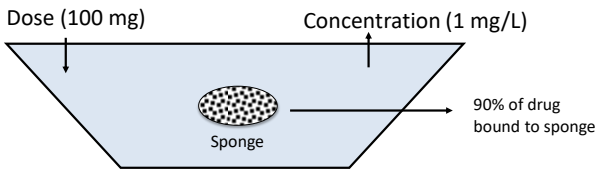
Slide 7

Apparent volume of distribution (V_D)

- Reasons why V_D is not physiological
  - Binding to tissues
    - Have high V_D
    - e.g. Digoxin binds to Na^+/K^+ ATPase
  - Binding to plasma proteins
  - Partitioning into tissues

Slide 8

Sponge model of V_D



V_D = amount/concentration = 100 mg / 1 mg/L = 100 L

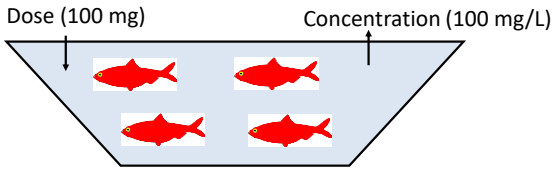
Slide 9

Apparent volume of distribution (V_D)

- Reasons why V_D is not physiological
  - Binding to tissues
  - Binding to plasma proteins
    - V_D is misleading ("red herring")
      - Bound drug is pharmacologically inactive
    - e.g. warfarin to albumin, lignocaine to $alpha_1$-acid-glycoprotein
  - Partitioning into tissues

Slide 10

Red Herring Model



V_D = dose/concentration = 100 mg / 100 mg/L = 1 L

Slide 11

V_D of plasma protein bound drugs

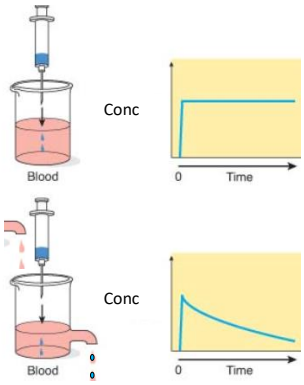
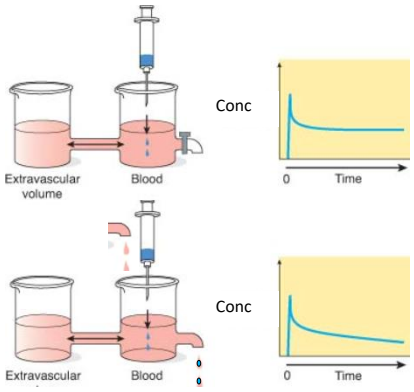
- Many drugs are highly plasma protein bound
  - e.g. warfarin 99% bound to albumin
- Plasma concentrations of warfarin
  - Total = 1 mg/L
  - Bound = 0.99 mg/L
  - Unbound = 0.01 mg/L
- Apparent V_D for a 10 mg dose of warfarin
  - Total = 10 mg / 1 mg/L = 10 L
  - Unbound = 10 mg / 0.01 mg/L = 1000 L

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

Slide 13	## Apparent volume of distribution (V_D) • Reasons why V_D is not physiological – Binding to tissues – Binding to plasma proteins – Partitioning into tissues • Lipophilic drugs into fat – e.g. thiopental – May lead to dosing problems in obese patients where fat content is much higher • Drug adsorption onto bone – e.g. tetracycline, bisphosphonates		
Slide 14	## Physiological Basis of V_D: examples • Warfarin: $V_D \approx 10$ L – Less than extracellular fluid, larger than plasma volume – Highly plasma protein bound • Gentamicin: $V_D \approx 16$ L – Similar to extracellular fluid – Highly ionised, low plasma protein binding		
Slide 15	## Physiological Basis of V_D: examples • Theophylline: $V_D \approx 35$ L – Similar to total body water – Non-polar, low plasma protein binding • Digoxin: $V_D \approx 500$ L – Na^+/K^+ ATPase binding – Muscle, kidney, nervous tissue		

Slide 16	**Pharmacokinetic compartments** • Apparent central compartment volume – Instantaneous distribution • Apparent tissue compartment volume – Delayed distribution – Depends on tissue binding and partition		
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.		.
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.		

Slide 19

Distribution rate

- Distribution half-life
  - Minutes
    - e.g. thiopental
  - Hours
    - e.g. digoxin
  - Days
    - e.g. lithium

Slide 20

Importance of V_D

- Can be used to calculate loading dose (LD)
- V_D influences
  - Time to reach steady-state
  - Time for all the drug to be eliminated
- V_D does not influence the steady state conc (C_{ss})
- C_{ss} is determined by
  - Clearance of the drug
  - Rate of input

Slide 21

Loading dose (LD)

- Initial dose administered to achieve a target concentration rapidly
  - Dependent on V_D
  - Helps to fill bath (V_D) faster to rapidly achieve the target concentration
  - The bigger the V_D the higher the dose required to achieve target concentration

  Loading dose (mg) = V_D (L) x target concentration (mg/L)

- If no loading dose is used, the volume takes time to fill up, so the larger the V_D 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

Slide 22

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_D 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)