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Rational Dose Prediction

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland, New Zealand

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Pharmacology

φάρμακον
pharmakon

Medicine Poison Magic Spell

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Pharmacology is derived from a Greek word (pharmakon). The Greeks used this word to mean a medicine, a poison or a magic spell.

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Pharmacokinetics Pharmacodynamics

Treatment

Rx = *Recipe*
or
Jupiter Symbol

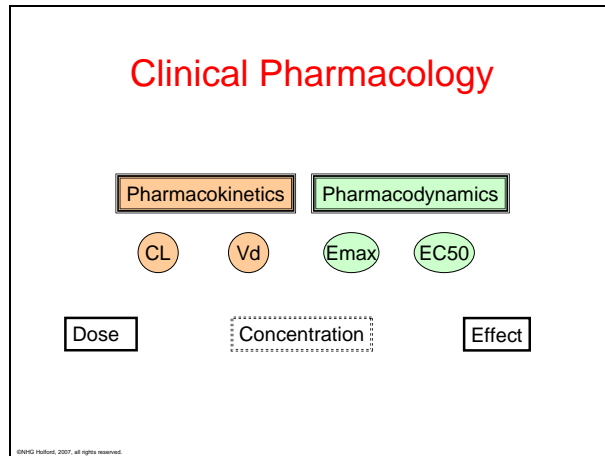
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PKPDRX

What does this mean?

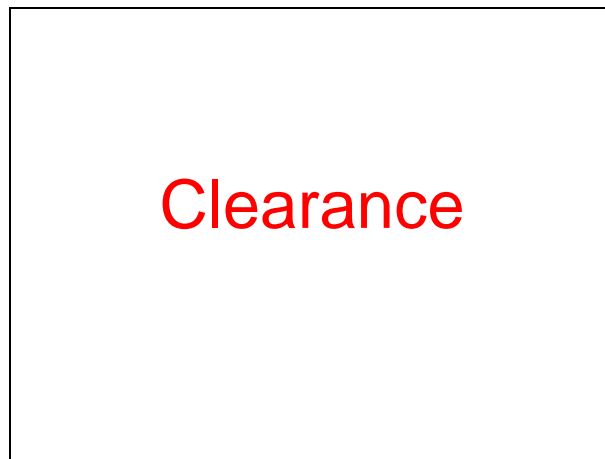
PK = Pharmacokinetics: What the body does to the drug
PD=Pharmacodynamics: What the drug does to the body
Rx=Treatment: What the prescribed and patient need to know.

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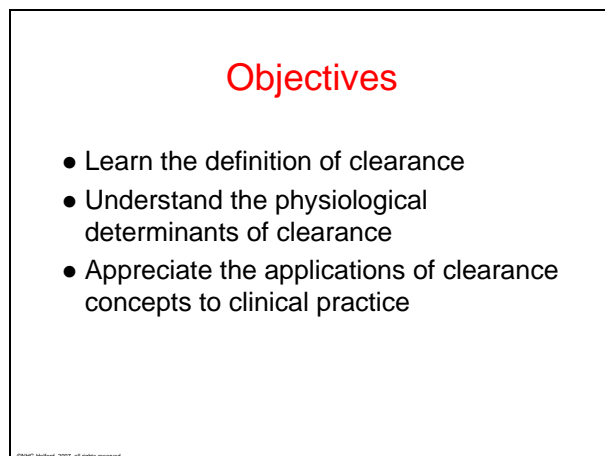
Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (Vd). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (EC50).

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Clearance is the most important pharmacokinetic parameter.

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Clearance

Clearance describes the relationship between concentration and the rate of elimination of drug from the body

$\text{Rate Out} = CL \cdot \text{Conc}$

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The definition of clearance (CL) links drug concentration to the rate of elimination (rate out). Note that elimination and clearance are NOT the same thing.

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Theophylline Target Concentration

Clin. Pharmacokinet. 25 (6): 495-505, 1993

Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomised Concentration-Controlled Trial

Nicholas Holford¹, Peter Black¹, Ron Couch², Julia Kennedy³ and Robin Briant¹

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

- How can a target concentration of 10 mg/L be maintained?

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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 maintain the concentration at the target?

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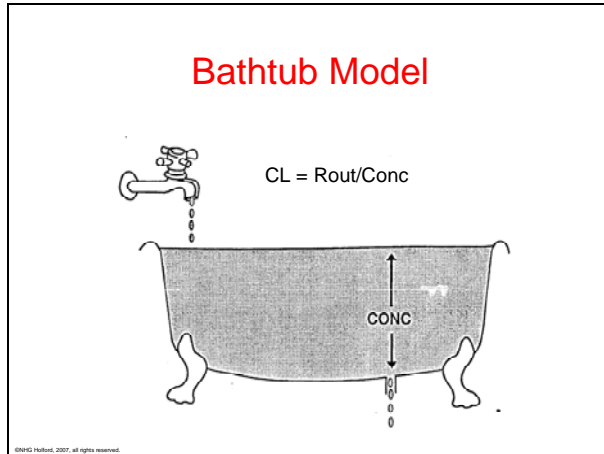
Maintenance Dose Rate

- At steady state
 $\text{Rate Out} = \text{Rate In}$
- Therefore
 $\text{Rate In} = CL \cdot \text{Concentration}$
 $\text{mg/h} = \text{L/h} \cdot \text{mg/L}$
 $30 \text{ mg/h} = 3 \text{ L/h} \cdot 10 \text{ mg/L}$

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Maintenance dose rate can be predicted if the target concentration and the drug clearance are known. Steady state drug concentrations are maintained when the rate of drug administration (rate in) is equal to the rate of elimination (rate out). Using the definition of clearance we can predict the steady state rate in. Note the units of clearance are typically L/h and concentration is mg/L. Maintenance dose rates are then readily predicted with units of mg/h.

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The bathtub provides a physical model to explain how clearance determines drug elimination.

This bathtub has fixed rate of water flowing in from the tap (rate in = 4 drops/unit time).

Water is lost from the bathtub at the same rate (rate out = 4 drops/unit time) which keeps the bath water level constant (steady state).

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Physiological Basis

- Liver Blood Flow
 - » 90 L/h Upper limit for liver metabolism
- Kidney Blood Flow
 - » 70 L/h Upper limit for kidney elimination
 - » Glomerular Filtration
 - 6 L/h All drugs
 - » Tubular Secretion
 - Variable

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A key factor determining the size of clearance is the blood flow to an organ.

The organ clearance cannot be any bigger than the blood flow rate. Note that clearance and blood flow are in the same units of volume/time (usually expressed as L/h) so they can be directly compared.

The liver is the largest single organ responsible for drug clearance. It has a typical blood flow of 90 L/h/70 kg. The main clearance mechanism by the liver is enzyme metabolism but some drugs are also excreted unchanged in the bile. Biliary excretion does not necessarily mean elimination because drug excreted in the bile can be re-absorbed in the small intestine.

The kidneys together have a combined blood flow of 70 L/h/70kg but few drugs have renal clearance approaching renal blood flow. All drugs (except for some large protein molecules) are filtered through the glomerulus but most are reabsorbed either passively or by active uptake mechanisms. Polar molecules are less likely to be re-absorbed and are excreted in the urine. The upper limit on renal clearance by glomerular filtration is the glomerular filtration rate (6 L/h/70kg). Some molecules e.g. weak acids like penicillin, are actively secreted by the tubules and can have clearances approaching renal blood flow.

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Physiological Basis

- **Very Rapid**
 - » Glyceryl trinitrate 150 L/h
 - plasma, liver, etc
- **Rapid**
 - » Morphine 60 L/h
 - liver

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Glyceryl trinitrate is used to treat angina. It is a very unstable molecule (it is an explosive when formulated differently). It breaks down in many tissues of the body and its clearance is not limited by blood flow to a single organ. Morphine is metabolized extensively in the liver and its clearance approaches liver blood flow. For this reason one can predict it will be extensively extracted from the blood as it passes through the liver.

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Physiological Basis

- **Medium**
 - » Gentamicin 6 L/h
 - Kidney
 - » Digoxin 9 L/h
 - Kidney and Liver

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Gentamicin is eliminated mainly by glomerular filtration so its clearance is about 6 L/h. Digoxin is cleared both by glomerular filtration but also by metabolism in the liver.

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Physiological Basis


- **Slow**
 - » Theophylline 3 L/h
 - Liver
- **Very Slow**
 - » Warfarin 3 L/day
 - Liver

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Theophylline is mainly metabolized by the liver but its clearance is low in relation to liver blood flow. Only a small fraction is extracted as blood passes through the liver. Renal elimination of theophylline is negligible. Warfarin has very slow clearance by liver metabolism.


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Concentration Dependent Clearance



$$R_{out} = \left[\frac{V_{max}}{K_m + C} \right] \cdot C$$

Mixed Order



$$R_{out} = \left[\frac{V_{max}}{K_m + C} \right] \cdot C$$

Zero Order

$$R_{out} = \left[\frac{V_{max}}{K_m + c} \right] \cdot C$$

$$R_{out} = CL \cdot C$$

First Order

$$R_{out} = V_{max}$$

Zero Order

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The order of a chemical reaction can be defined in terms of the number of reactive species determining the rate of the reaction.

Enzymatic reactions are typically saturable and can be described in terms of the maximum rate of elimination (V_{max}) and the concentration producing 50% of V_{max} (K_m).

Most enzymatic drug metabolism appears to be driven only by the drug concentration. If concentration is small in relation to K_m then the elimination rate will appear to be first-order i.e. linearly dependent only on concentration. If concentrations are large in relation to K_m then the elimination rate will appear to be independent of concentration and this is called a zero-order reaction.

Concentrations that are neither small nor large in relation to K_m will give rise to a mixed-order reaction. The mixed-order reaction should be considered as the general case for all drugs eliminated by metabolism. The first-order approximation is very common. True zero-order elimination does not occur but is approximated at very high concentrations.

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Applications

- Maintenance Dose

Maintenance Dose Rate = $CL \cdot \text{Target Conc}$

- Half-Life

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

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The main clinical application of understanding about clearance is for prediction of the maintenance dose rate. A second useful application is the ability to calculate the half-life. This requires the volume of distribution (V_d) to be known as well as clearance.

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Applications

- Additional elimination processes
 - » Haemodialysis
 - » Haemoperfusion
 - » Gut adsorption (charcoal)

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The benefits of treatments intended to enhance elimination after poisoning can be evaluated by comparing the clearance by the treatment to the expected drug clearance without treatment.

Haemodialysis is the same procedure used for patients with renal failure.

Haemodialysis clearance is relatively low (e.g. theophylline is 4 L/h).

Haemoperfusion involves passing blood through a cartridge designed to adsorb the drug. Haemoperfusion clearance can be double that of haemodialysis (e.g. theophylline is 9 L/h) but there is wide drug to drug variability (Cutler RE, Forland SC, Hammond PGS, Evans JR. Extracorporeal Removal of Drugs and Poisons by Hemodialysis and Hemoperfusion. Annual Review of Pharmacology and Toxicology 1987;27(1):169-191.)

Adsorption of drug in the gut by activated charcoal can enhance elimination by preventing primary absorption and re-absorption from drug passing from the

body passively back into gut fluids.
Activated charcoal can double
theophylline clearance from 3 L/h to 6
L/h.

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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
- 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

$$\text{Amount} = Vd \cdot \text{Conc}$$

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The definition of apparent volume of distribution (V_d) 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.

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Loading Dose

$$\text{Amount} = Vd \cdot \text{Conc}$$

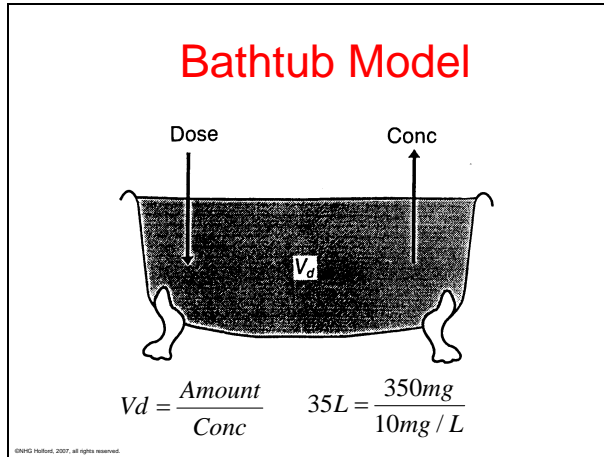
$$\text{mg} = \text{L} \cdot \text{mg/L}$$

$$350 \text{ mg} = 35 \text{ L} \cdot 10 \text{ mg/L}$$

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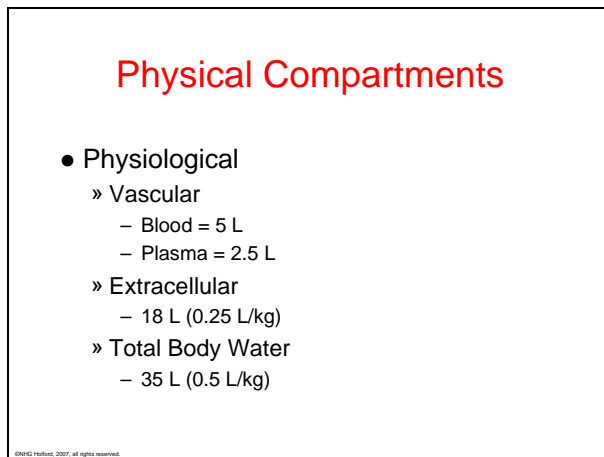
The loading dose can be predicted if the target concentration and the drug apparent volume of distribution are known. Note the units of volume are typically L and concentration is mg/L. Loading doses are then readily predicted with units of mg.

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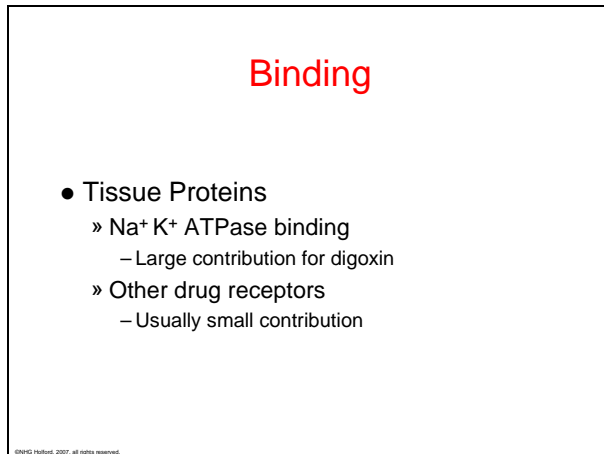
The bathtub provides a physical model to explain how physical factors can influence the apparent volume. In this example there is no loss of water from the bathtub. By putting a known amount of drug (the dose) into the bathtub and measuring the concentration it is easy to calculate the apparent volume.

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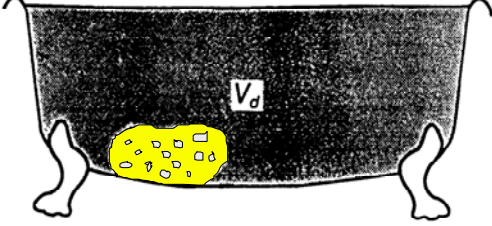
Apparent volume of distribution does not necessarily correspond to any physical compartment because of binding to tissues, binding to plasma proteins or partitioning into fat or adsorption onto bone.

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



$350L = \frac{350mg}{1mg / L}$

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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 lower than the physical volume.

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Binding

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

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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.

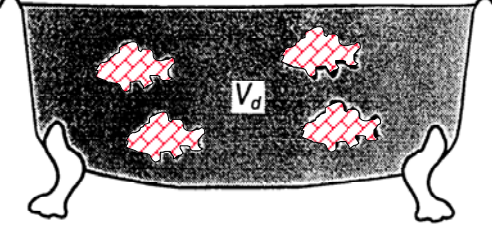
http://en.wikipedia.org/wiki/Red_herring

The phrase **red herring** has a number of specific metaphorical meanings, all sharing a general concept: something being a diversion or distraction from the original objective. These include: a type of logical fallacy in which one purports to prove one's point by means of irrelevant arguments (see *Ignoratio elenchi*).

in adventure games, an item or object of no practical use; its purpose may be to frustrate the gamer who tries to find the intended use for it.

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"Red Herring" Model



$3.5L = \frac{350mg}{100mg / L}$

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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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Apparent Volume of Distribution Physiological Basis

- Tiny
 - » Warfarin 10 L
 - Less than ECF, Greater than Blood
 - Plasma protein binding
- Small
 - » Gentamicin 18 L
 - Approx. ECF

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Warfarin has a very small apparent volume 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. This indicates that it does not bind extensively to tissues.

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Apparent Volume of Distribution Physiological Basis

- Medium
 - » Theophylline 35 L
 - Total Body Water
- Large
 - » Digoxin 500 L
 - Na⁺ K⁺ ATPase binding
 - Muscle, kidney, nervous tissue

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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.

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Applications

- Loading Dose

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

- Half-Life

$$T_{1/2} = \frac{0.7 \cdot Vd}{Cl}$$

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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.

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Rational Dosing and the Target Concentration

Target	Dose Model
Initial Peak	Loading Dose= $\text{Target Conc} \times \text{Volume of distribution}$
Average Steady State	Maintenance Dose Rate= $\text{Target Conc} \times \text{Clearance}$

Rational Dose prediction requires a Target Concentration

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The Target Concentration Approach

Science Clinical Pharmacology

Models Pharmacokinetics Pharmacodynamics

Clinical Goal Target Dose ← Target Concentration ← Target Effect

Holford NHG. The target concentration approach to clinical drug development. Clinical Pharmacokinetics 1995;29(5):287-91

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The target concentration approach starts by identifying the desired clinical benefit of treatment. The size of the drug effect required to achieve clinical benefit is the target effect. With a pharmacodynamic model to link concentrations and effects it is then possible to predict the target concentration which will produce the target effect. The final step is to apply a pharmacokinetic model to predict the dose needed to reach the target concentration.

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