THE UNIVERSITY OF MELBOURNE

Melbourne Veterinary School

METABOLISM
Introduction to Pharmacokinetics 2
What does the body do to drugs?

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VETS30017/VETS90125

OBJECTIVES PHARMACOKINETICS PART 2

- Explain the processes of distribution and explain how a “Volume of distribution” is calculated
- Describe the concept of **first pass hepatic metabolism**, and how, along with extent of absorption, it influences the **biovailability** of drugs administered orally
- Describe how the elimination of drugs is dependent on metabolism and excretion, and how these two processes work in concert to result in elimination
- Describe what is meant by the term **half life of elimination**
- Explain how **withholding period** is calculated
- Explain the term **maximum residue level** (MRL)

"Volume of distribution"

- The volume of body water in which a drug "appears" to be dissolved, after it has distributed throughout the body
- Vd = X/C
- Where X = amount administered
- And C-= concentration at time of administration
- **Vd is not a REAL volume- it is an apparent one**

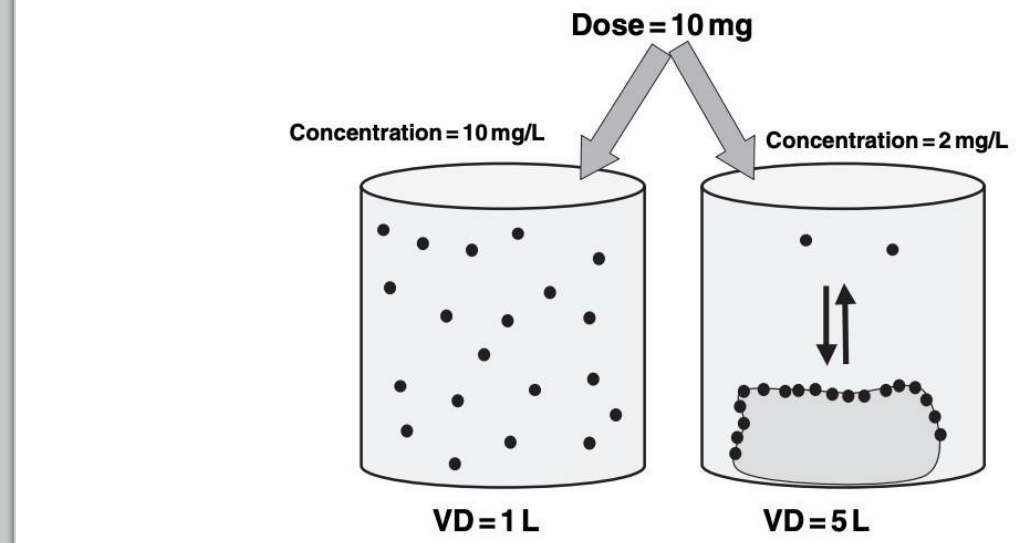


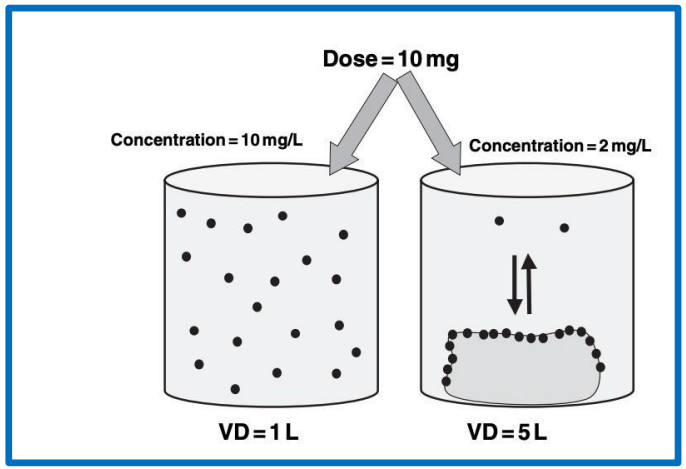
Fig. 2. A simplistic system to introduce the concept of volume of distribution. The same amount of drug (10 mg) is dissolved in the same volume of water (1 L). For the left beaker the water concentration is 10 μg/mL and when applying Eqn 1 in the text, the computed apparent volume of distribution of the drug in the left beaker is 1 L (which corresponds to the actual volume of water in the beaker). In the right beaker, there is charcoal that can fix part of the drug, which is divided between water and charcoal. The water concentration is here of only 2 μg/mL and applying Eqn 1 of the text gives an apparent volume of distribution of 5 L, i.e. five times the actual volume of water.

J Vet Pharmacology and Therapeutics. 27, 441–453, 2004
P. L. TOUTAIN & A. BOUSQUET-MÉLOU

Why is Vd important?

- Because it tells you how much drug you need to give to get a certain concentration in the plasma

- If a drug bind extensively to tissues, Vd for the drug can be very high- much greater than the volume of the patient (or total body water)!



Examples of Vd

- Plasma volume .06L/kg
  - A drug that is a protein or is bound to plasma protein will have a Vd approximating this value
  - Eg aspirin 0.1L/kg
- Extra cellular fluid volume (.2L/kg)
  - Drug exits blood vessels
  - Unable to cross cell membranes
  - Distributes evenly in body
  - Eg mannitol Vd = .2L/kg
- Total body water volume .6L/Kg
  - As for ECF but drug can cross cell membranes
  - Eg ethanol Vd= .6L/Kg

Some really large Vd's!

- Morphine 2L/Kg
- Digoxin 6L/Kg
- Fluoxetine 35 L/Kg
- These drugs bind extensively to tissues!

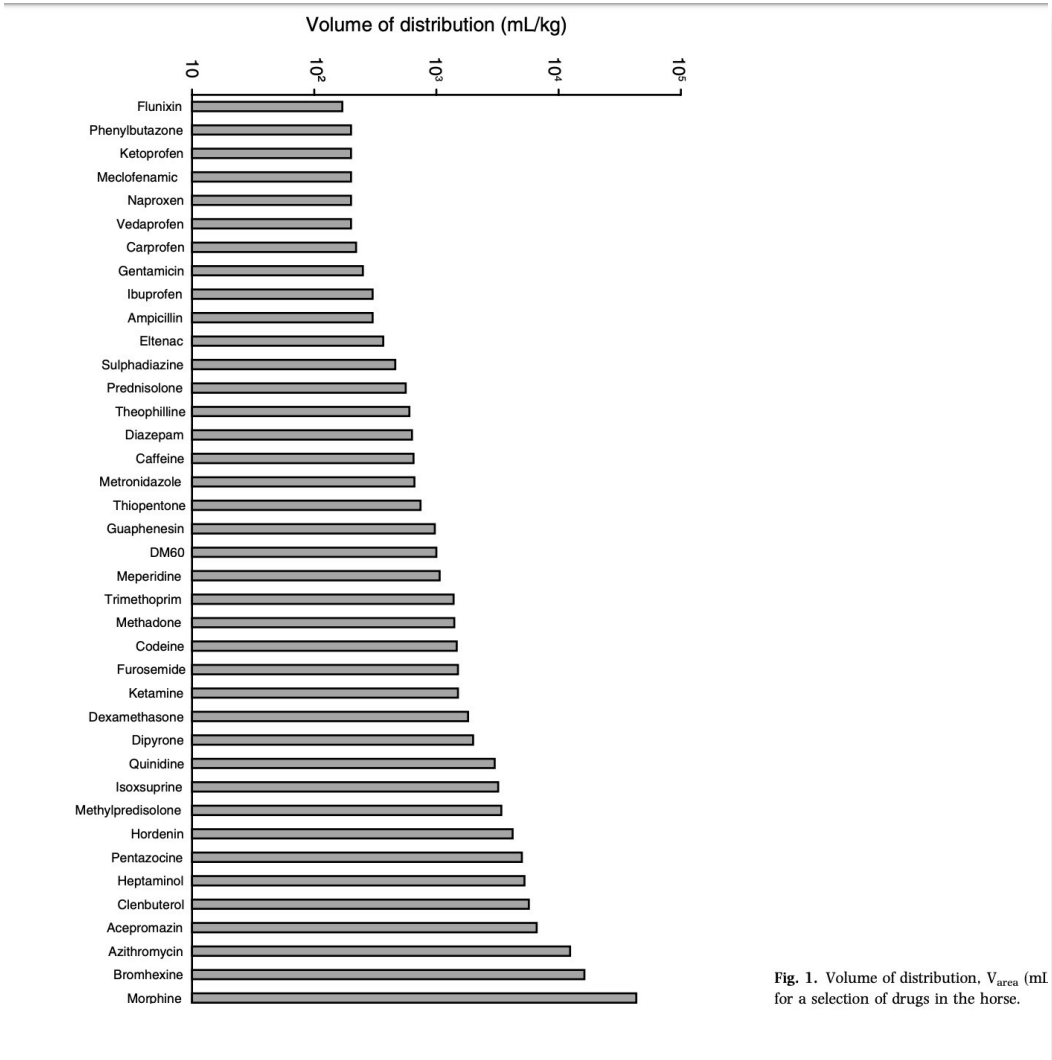


Fig. 1. Volume of distribution, V_{area} (mL
for a selection of drugs in the horse.

Example: Volume of distribution for a range of drugs in the horse

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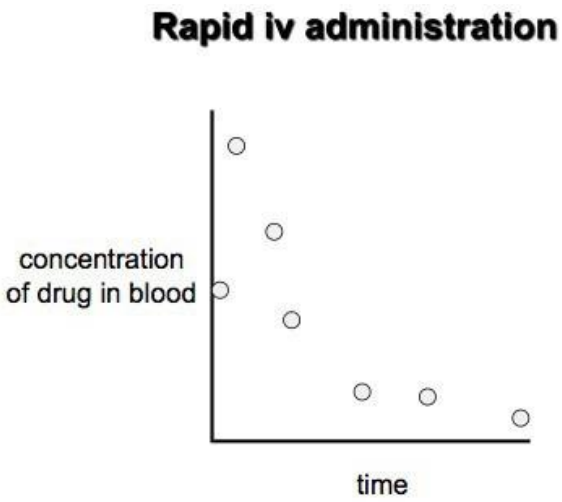
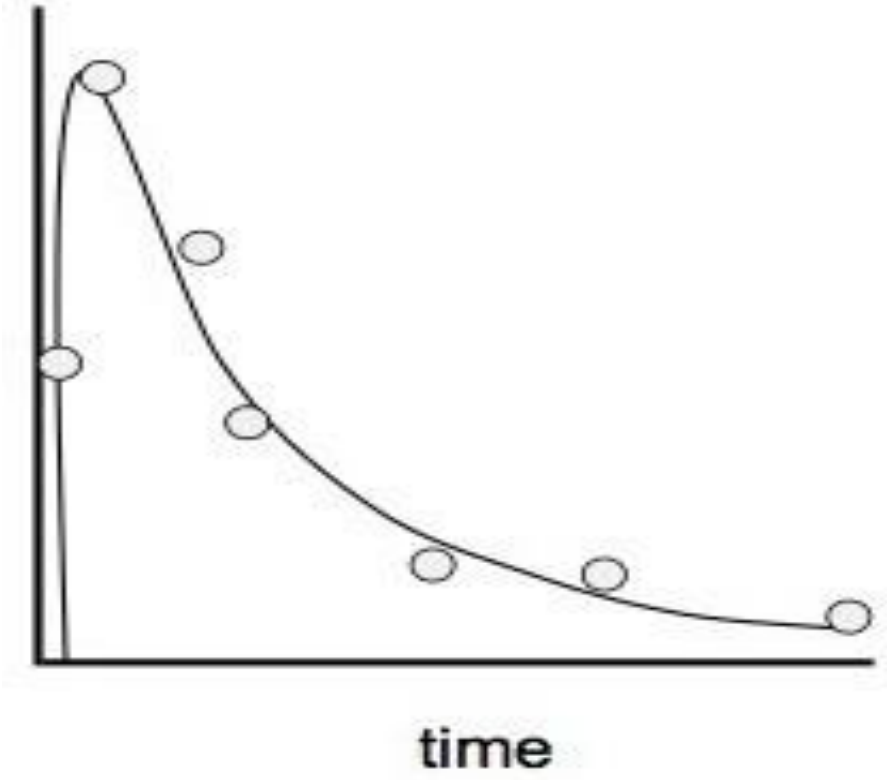
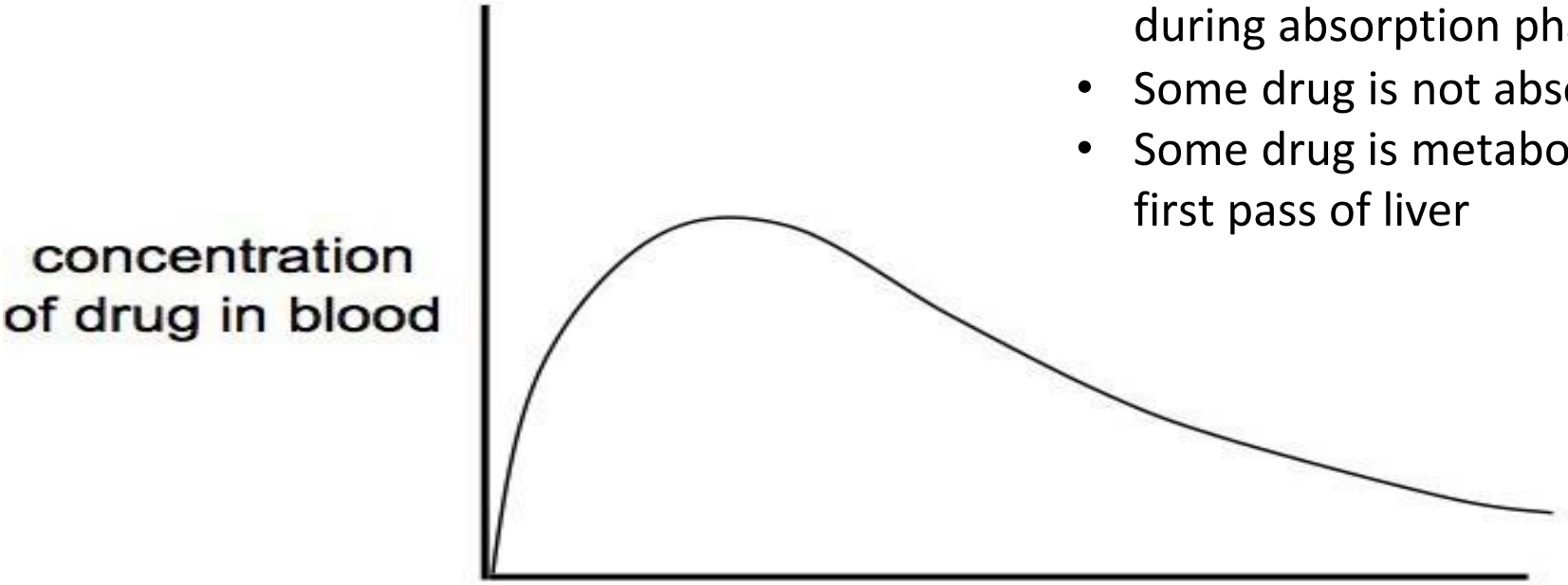
A D METABOLISM E

What happens when we give a single rapid I/V injection?





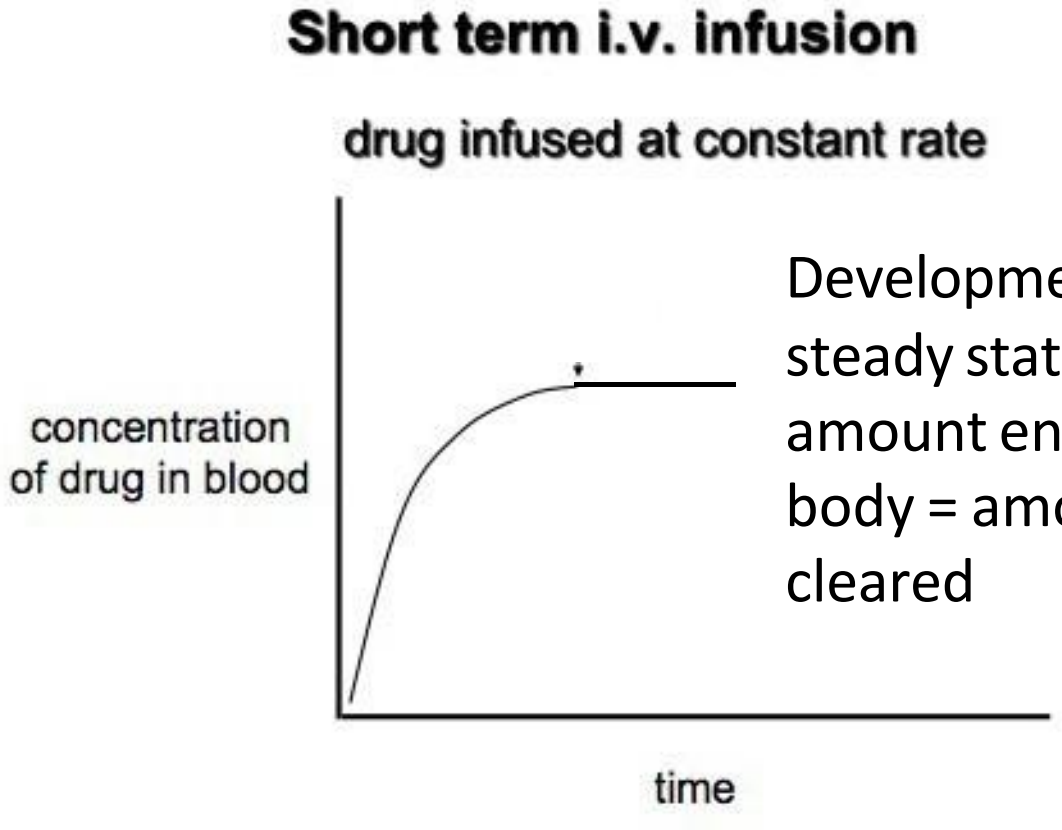
What happens if we give an oral dose?



Peak blood concentration is not as high:

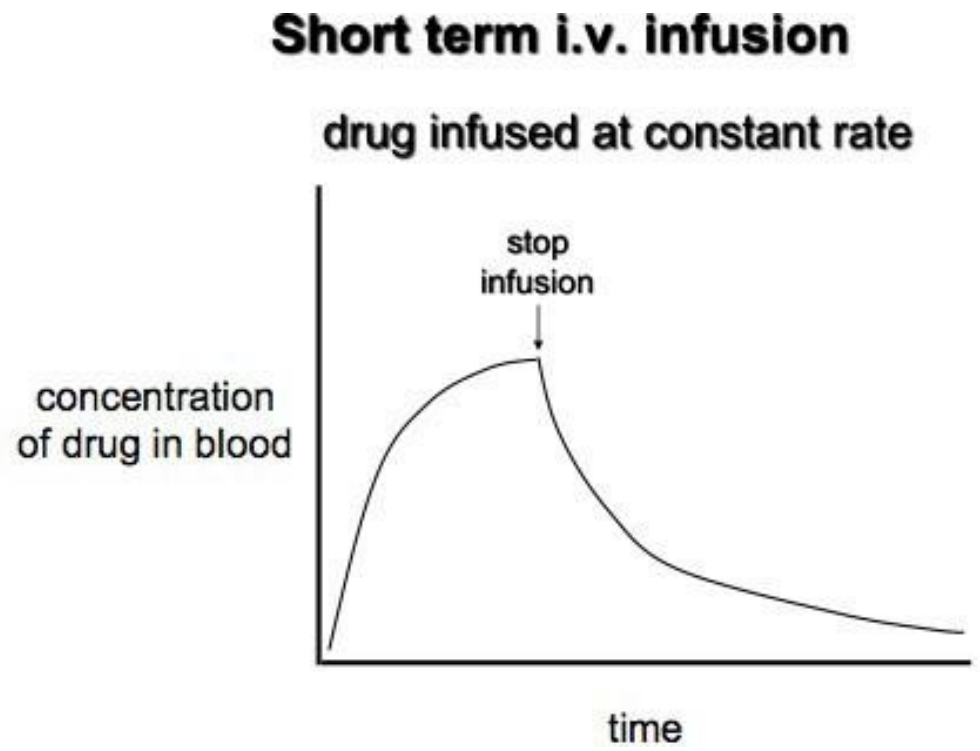
- Some elimination occurs during absorption phase
- Some drug is not absorbed
- Some drug is metabolised in first pass of liver

What happens to blood levels with constant infusion?



Development of a steady state- where amount entering body = amount being cleared

What happens when we stop the infusion (or oral dosing?)



Drug disappears from the plasma either because it is **DISTRIBUTED** to tissue or because it is **METABOLISED and EXCRETED**

Drug half-life

- Once drug administration stops, there will be a decline in plasma concentration…and the time taken for it to fall by a half is the **half-life**

- Half-life is **long** if the drug distributes very widely in tissues or if clearance is slow

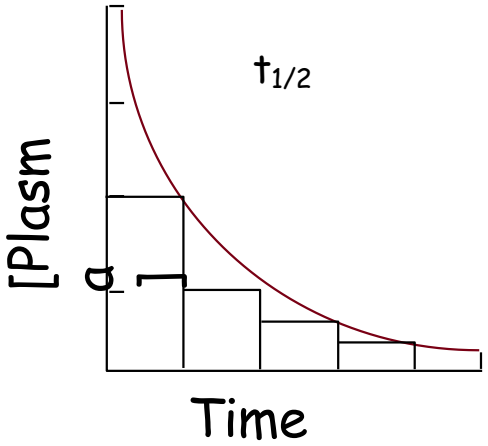
- Half life is also long if the drug is given in a depot form that is released very slowly from the injection site

Duration of action: half life

- After a single dose, the longer the half-life, the longer the duration of action
- However, the duration is **not** doubled by giving twice the dose….because it is a **logarithmic** relationship (not linear)
- To double the duration would require 10x the dose - and that could be toxic
- With constant regular oral dosing of drug it takes 4 to 5 half-lives to reach steady state.
- Similarly, it will take 4 to 5 half-lives to clear the dug from the body

First- and zero-order kinetics

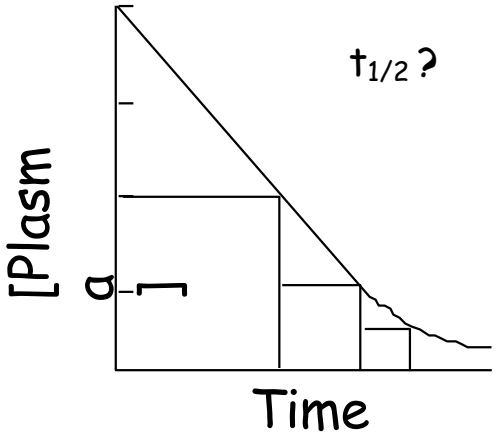
First-order



Rate proportional
To plasma concentration

Constant time for
[plasma] to fall by half

Zero-order

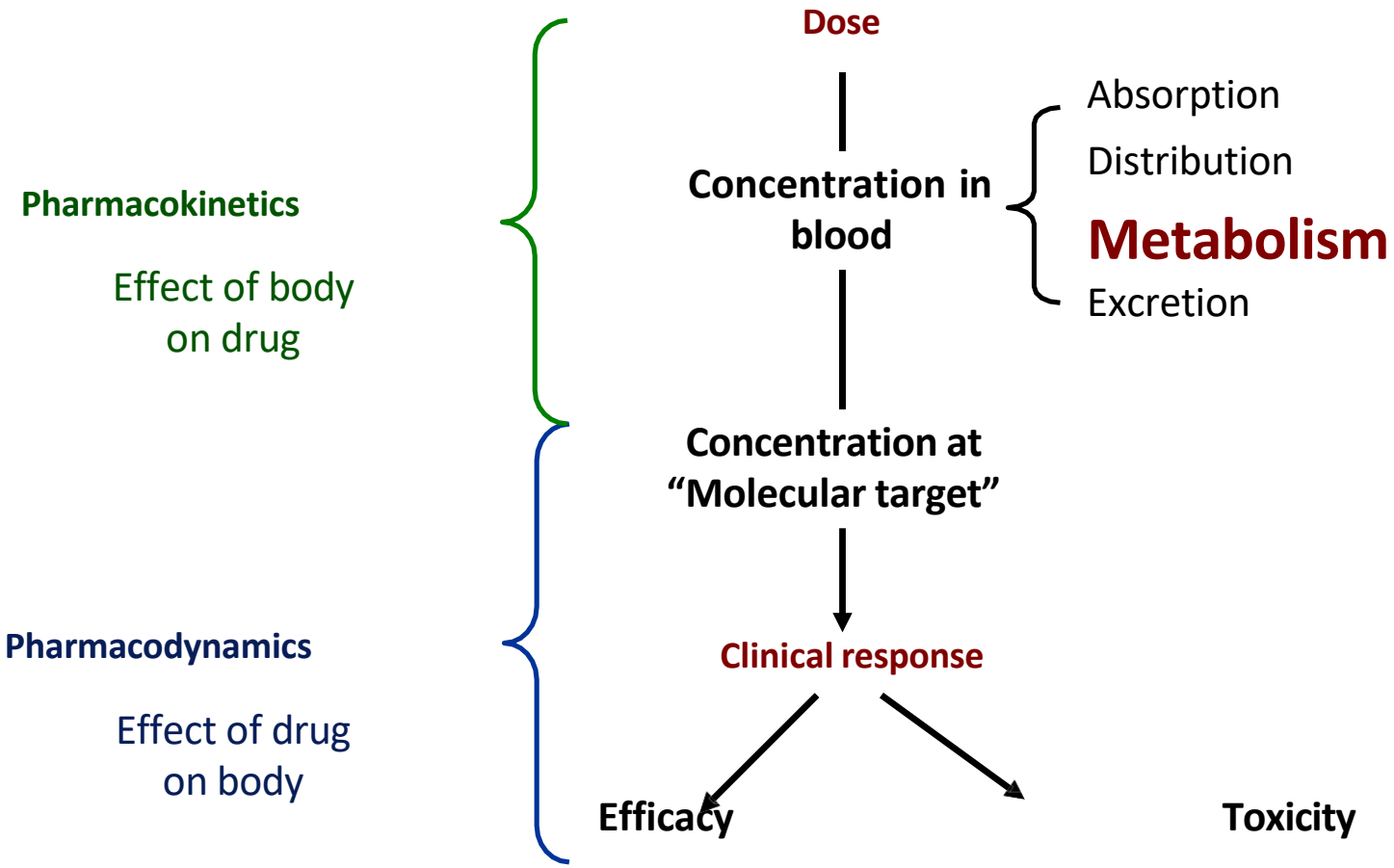


Rate NOT proportional
To plasma concentration

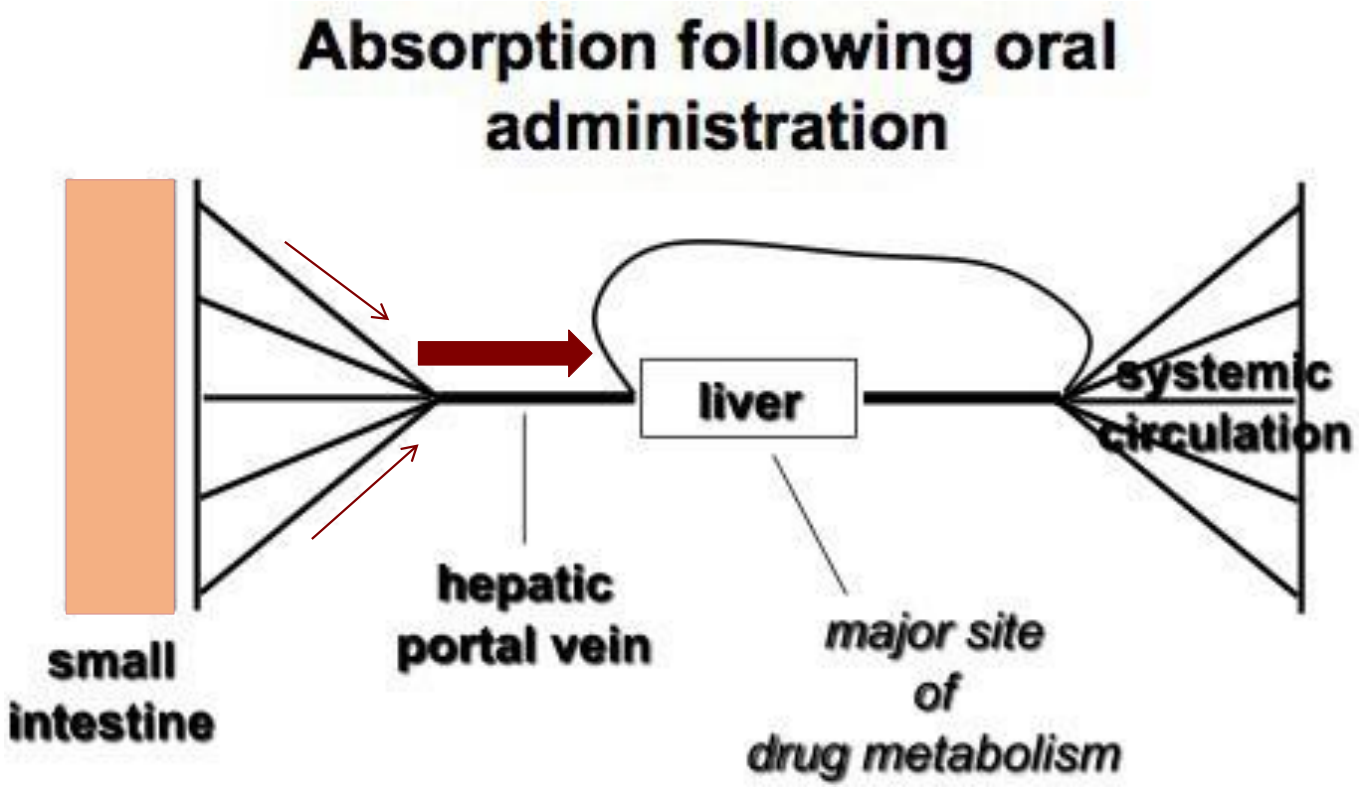
Variable time for
[plasma] to fall by half

Half life= the time taken for plasma concentration to fall by a half

Getting the dose right: METABOLISM



Metabolism and the first pass effect



Metabolism: & the first pass effect

- Most drugs go to the **liver** after being absorbed from the upper gastrointestinal tract
- The liver is the major site of drug metabolism in the body
- There is also cytochrome P450 (superfamily of metabolic enzymes) in the **gut wall**
- The 'destruction' of drugs soon after absorption is called "**first pass metabolism**"
- How much of the drug "escapes" metabolism at this first pass determines BIOAVAILABILITY of the drug

Bioavailability

- Bioavailability is the proportion of an oral dose of a drug that reaches the systemic circulation

- 60% bioavailability means that 60% of the ingested dose reaches the systemic circulation

…(*and 40% is either metabolised the first time it passes through the liver, or is never absorbed from the gut*)

Reminder… what are the factors that drugs might limit absorption from the gut??

Metabolism in the liver

- **Metabolism occurs in two phases** (that can occur at the same time)
- **Phase 1:**
  - Creates a reactive site
  - Increases water solubility by hydrolysis, reduction or oxidation
  - Involves Cytochrome p450 superfamily of enzymes
- **Phase 2**
  - **Synthetic** reactions that usually follow Phase 1 metabolism and add groups by conjugation to increase water solubility and reduce toxicity
    - Acetylation
    - Sulphation
    - Glucuronidation
    - Methylation

Decline from steady state

- It takes about **4 half-lives** for drug concentration to drop to zero (or close to it) after stopping administration
- This is the **mirror image** of the rise to steady state
- Keep this in mind when giving drugs to any production animal

Half-life is very important for drugs administered to production animals

- It tells us how long the farmer must wait after administration of the drug, before sending meat, milk or fibre products to market
- This is called the **withholding period**
- It may be up to **TEN half-lives** of the drug
- Withholding period will depend on the MAXIMUM RESIDUE LIMIT (MRL) for the product- the maximum permitted amount of drug in the animal product for human use

Imidacloprid for lice control

Withholding Periods

Wool - 6 months

Meat - 21 days

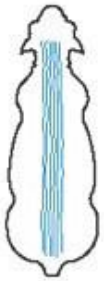
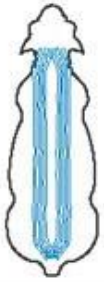
Milk - Not to be used on sheep producing milk for human consumption

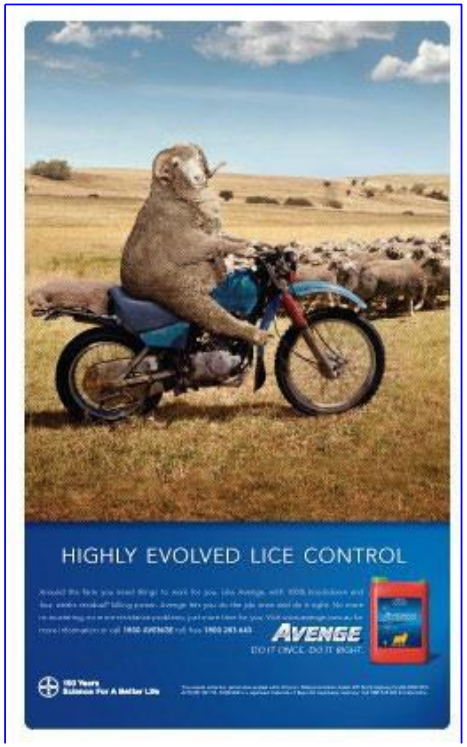
ESI - 63 day

Active Constituents

35g/L Imidacloprid

Dose Rate

Bodyweight (kg)	Dose (mL)	Method	Apply in the pattern below
Below 6kg	8	Single stripe	
6.0 - 8.0	12		
8.1 - 10.0	15		
10.1 - 12.5	20		
12.6 - 15	25		
15.1 - 20	30		
20.1 - 30	40		
30.1 - 55	60	Double stripe	
55.1 - 80	80		
80.1 - 100	90		



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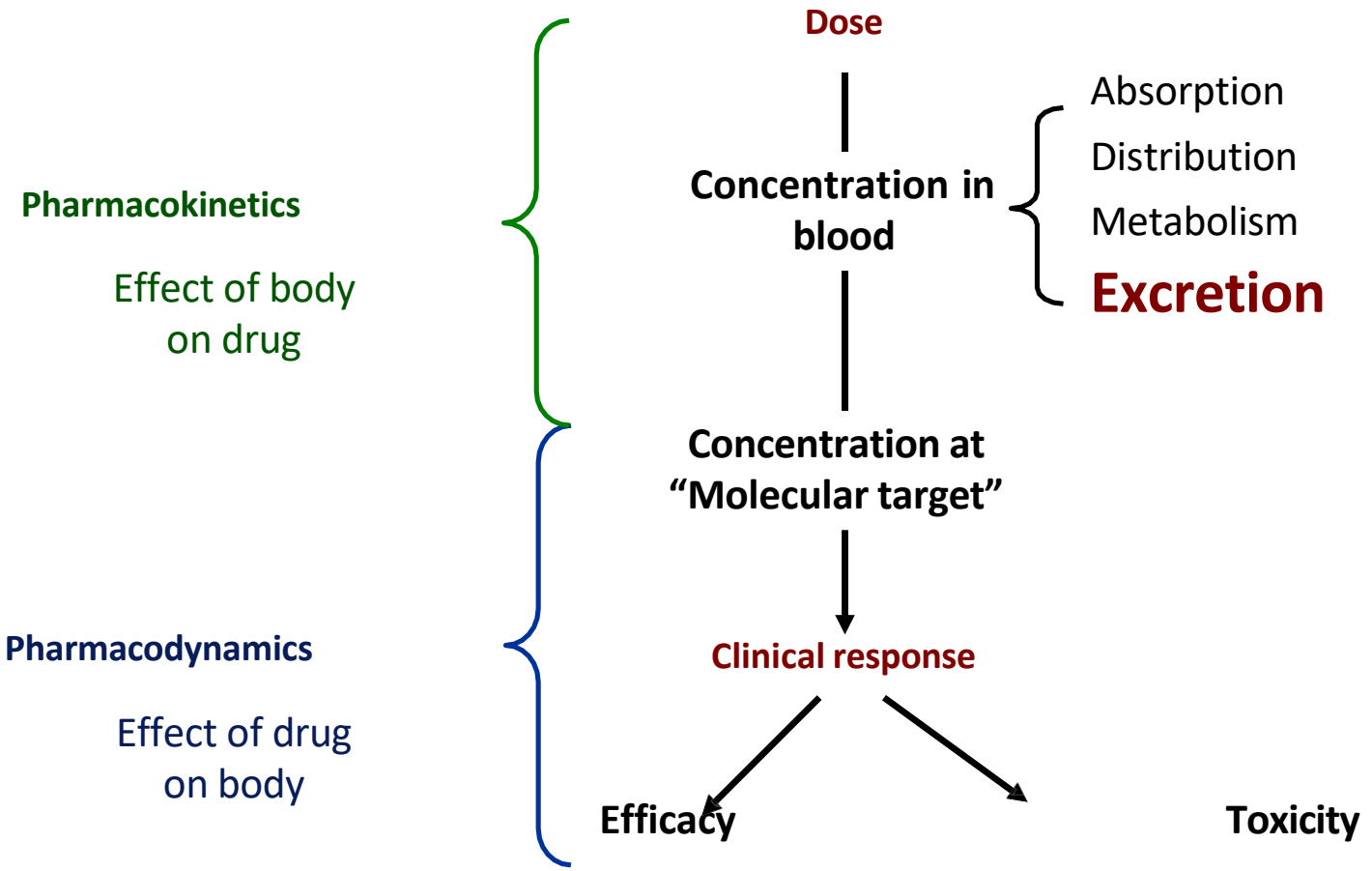
EXCRETION

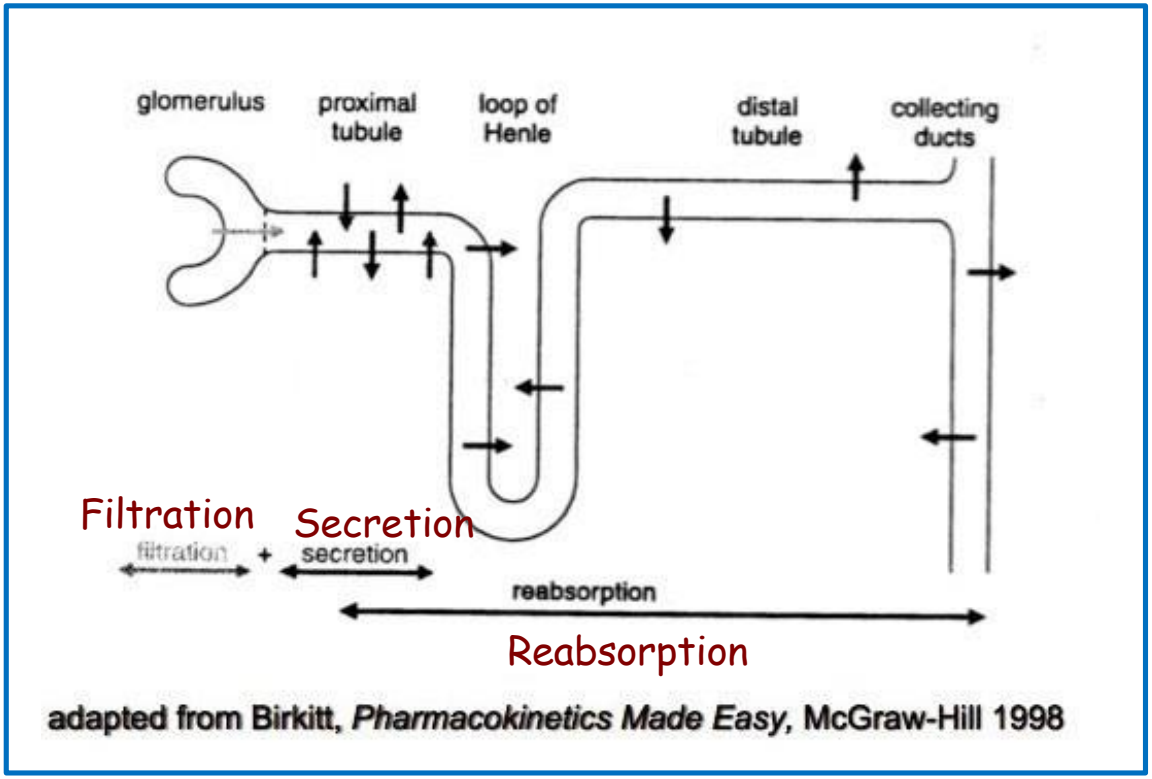
EXCRETION


Dose
Concentration in blood
Absorption
Distribution
Metabolism
Excretion
Pharmacokinetics
Effect of body on drug
Concentration at "Molecular target"
Clinical response
Pharmacodynamics
Effect of drug on body
Efficacy
Toxicity

Drug Elimination

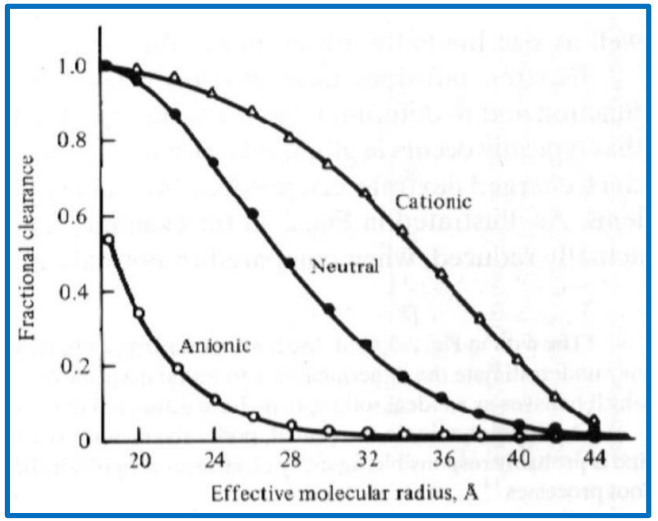
- Happens by:
  - excretion (mainly in the kidneys)
  - metabolism (mainly in liver… but also kidney)
- Usually a combination of both

- Renal excretion:
  - Glomerular filtration
  - Tubular secretion
  - Tubular reabsorption



Glomerular Filtration

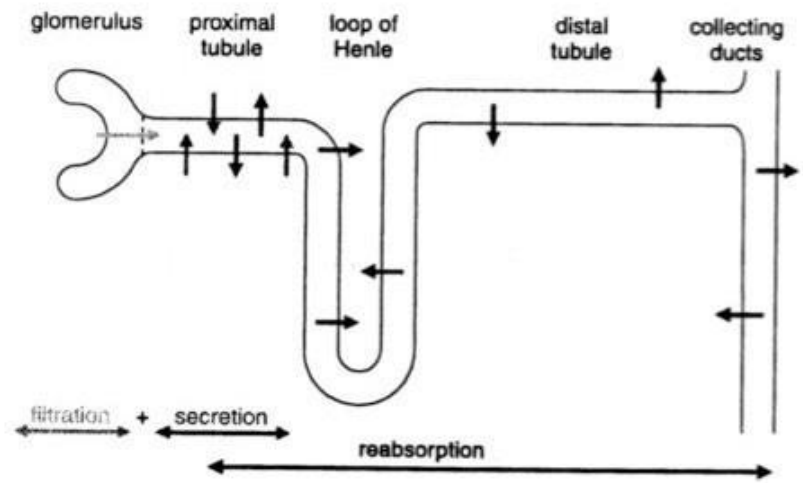
- Takes drugs ***out*** of body
- Passive filtration through glomerulus
- Relies on glomerular filtration rate (ie renal blood flow)
- Filtration also depends on:
  - plasma protein binding (bound drugs not filtered)
  - Molecular size
  - Charge.



Highly charged larger molecules have lower fractional clearance

Tubular Secretion

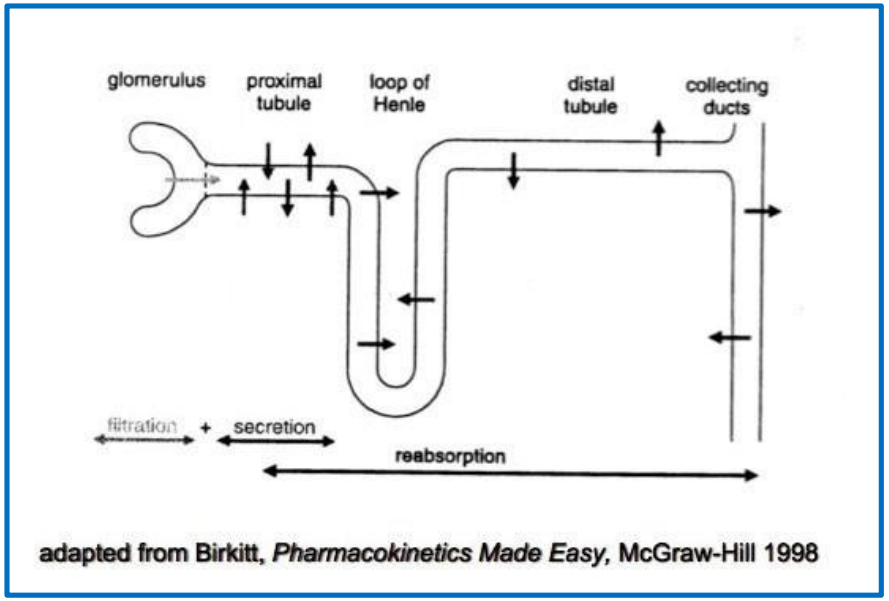
- Takes drugs ***out*** of blood
- Uses active transport carriers
- Can remove protein bound drugs
- Can be competitively inhibited



adapted from Birkitt, *Pharmacokinetics Made Easy*, McGraw-Hill 1998

Tubular Reabsorption

- Brings drugs ***back*** *in* blood
- Passive movement of drug across tubular membrane and peri-tubular capillary
- pH dependent – because only NON ionised (lipid soluble) drug will cross the tubular membrane

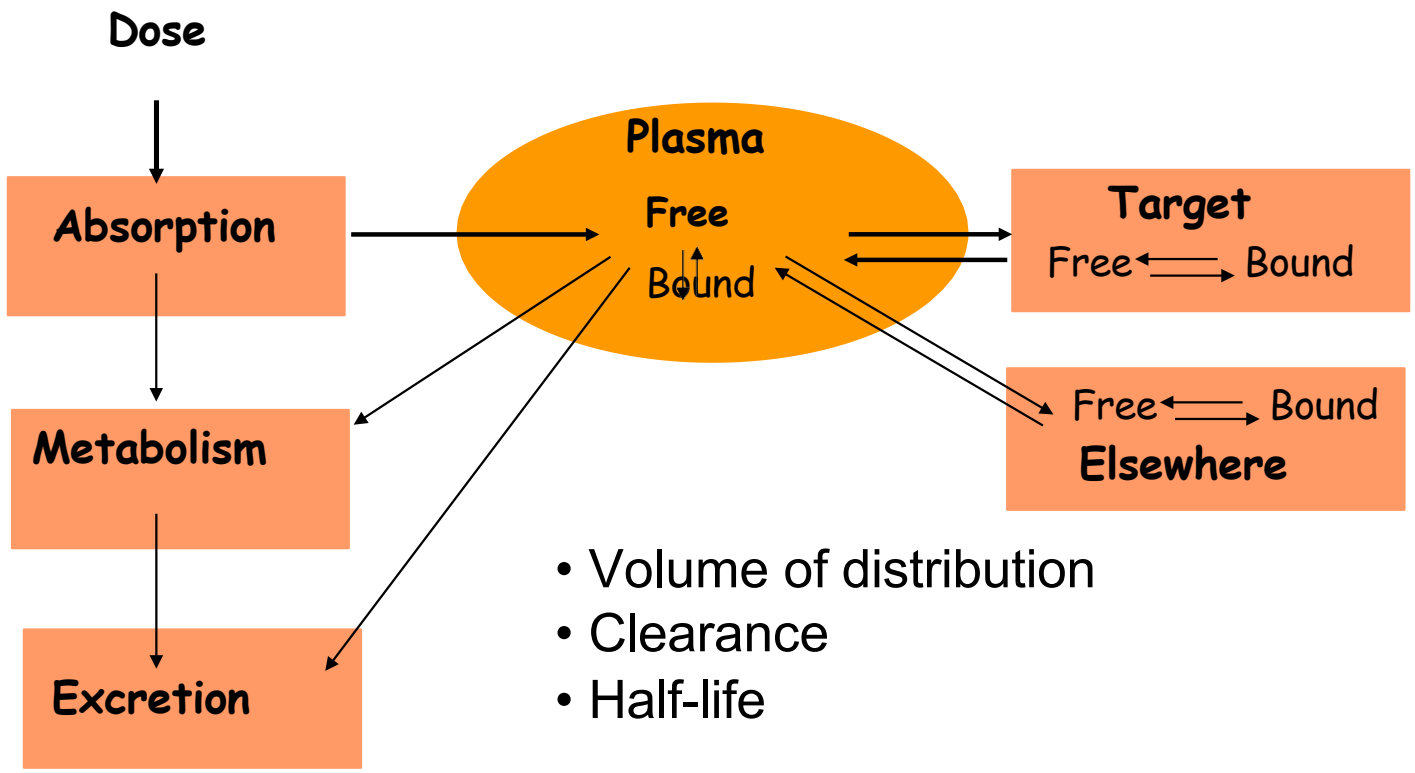


adapted from Birkitt, *Pharmacokinetics Made Easy*, McGraw-Hill 1998

Pharmacokinetics

What the body does to a drug

- parameters influencing concentration-time relationship

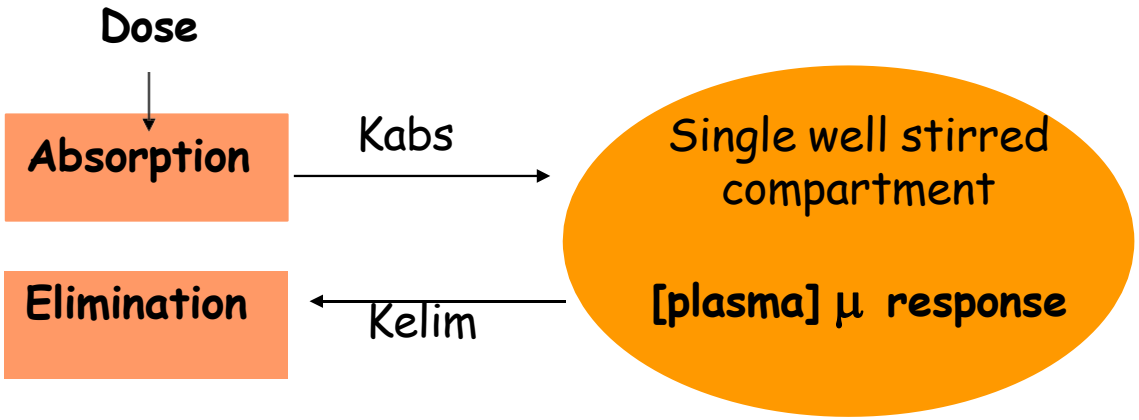


- Volume of distribution
- Clearance
- Half-life

Not only how much, but also how often!

Pharmacokinetics

Equilibria can simplify to ...



- Volume of distribution (Vd)
  - indication of extent of distribution, but not location
    - Initial dose
- Clearance (Cl)
  - irreversible removal of the drug (metabolism & excretion)
    - Steady state dose
- Half-life ($t_{1/2}$)
  - composite of Vd and Cl
    - Dose interval, time to steady state

Principles of Pharmacology

Where ?

Affinity &
selectivity

How much ?

Potency
& efficacy

How often ?

Absorption &
elimination

Pharmacodynamics

Pharmacokinetics

In SUMMARY

- What routes are used to administer drugs to animals?
- How are drugs moved across membranes?
- What are the limitations to absorption of drugs?
- How are drugs distributed in the body?
- Explain the term Volume of distribution (Vd)
- How are drugs broken down in the body?
- By what means are they eliminated?
- What is the half life of a drug?
- What does bioavailability mean?
- How is withholding time determined?
- What is the meaning of the term MRL (maximum residue limit)?