THE UNIVERSITY OF MELBOURNE

Melbourne Veterinary School

METABOLISM
Introduction to Pharmacokinetics 1
What does the body do to drugs?

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VETS30017/VETS90125

Introducing Noroclox…

What is *Noroclox DC Xtra* Intramammary suspension?

- What is the active ingredient and **how does it act?**
- How much is required? (**what is the dose**?)
- What else is in the preparation? (what are the excipients?)
- How is it administered?
- **How often** is it required to be administered?
- How long will it last? (**withdrawal periods**)
- What ill effects might it have? (**toxicity**)

What is *Noroclox DC Xtra* Intramammary suspension?

- What is the active ingredient and how does it act? **Cloxacillin- an antibiotic effective against gram positive bacteria**
- How much is required? (what is the dose?) **generally dose is calculated in mg/kg body weight**
- What else is in the preparation? (what are the excipients?) **in this case a base that "holds" the antibiotic in the mammary gland for an extended period of time**
- How is it administered? **Instilled into the teat canal**
- **How often** is it required to be administered? **Once at drying off**
- How long will it last? (withholding periods) **For meat 28 days, for milk 42 days**
- What ill effects might it have? (toxicity) **antibiotic sensitivity allergic reaction**

What is a drug?

- An exogenously administered substance that changes the function of the physiological system of an organism
- Most are not normally in the body
- e.g. therapeutic agents, poisons,
- Some may mimic or block endogenous (naturally occurring) substance in the body eg hormones, neurotransmitters
- May be used to kill microbes or parasites, treat inflammation, induce parturition, kill endo or ectoparasites, sedate the patient

Drug names

Most therapeutic drugs have both a **trade** name and a **generic** name

Trade	Generic
Panadol	paracetamol
Ventolin	salbutamol
Norclox	cloxacillin
Bomectin	ivermectin

Often different pharmaceutical companies make the same generic drug- and so market it under different trade names

Eg **Ivermectin** is marketed as:

Bomectin, Noramectin, Stromectol, Baymec

by different pharmaceutical companies

Who can administer drugs?

Depends on the classification of the drug (by APVMA)

- ***Schedule 2***. Only available from a pharmacy, veterinary surgery or licensed person (where a pharmacy or veterinary surgery is not available), but can be sold from open shelves and advertised. Eg anti parasitic drugs

- ***Schedule 3***. Only sold by authorised persons including veterinarians, and cannot be advertised except as a generic drug group.

- ***Schedule 4.*** Only sold (dispensed) on prescription – includes prescription animal remedies and prescription only medicines (registered for use in humans) eg antibiotics.

- ***Schedules 5, 6, 7***. Non-therapeutic chemicals in increasing order of toxicity (with some restrictions on the availability of S7 products). (eg herbicides)

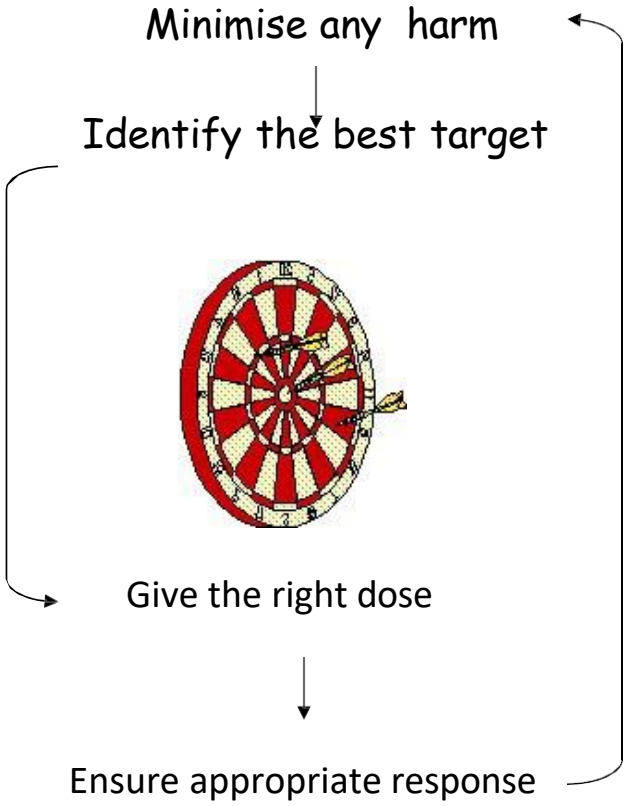
- ***Schedule 8.*** Substances with legitimate therapeutic uses, but which have addictive or abuse potential. (eg morphine)

Objectives- Pharmacokinetics PART 1

- Describe processes by which the body may influence the actions of a drug.
- Describe the difference between local and systemic **routes of administration**, and the advantages and disadvantages of each
- List the major components of pharmacokinetics – **administration, absorption, distribution and elimination**
- Explain the means by which drugs undergo absorption, allowing them to enter the systemic administration, in particular the role of lipid diffusion in crossing cell membranes
- Explain the processes of distribution, and the factors that limit distribution

Safe and effective drug use

- Objective
  - Do no harm / provide benefit
- Know where a drug acts
  - Predict response
- Know how much to give
  - How often to give?
  - Long term consequences?

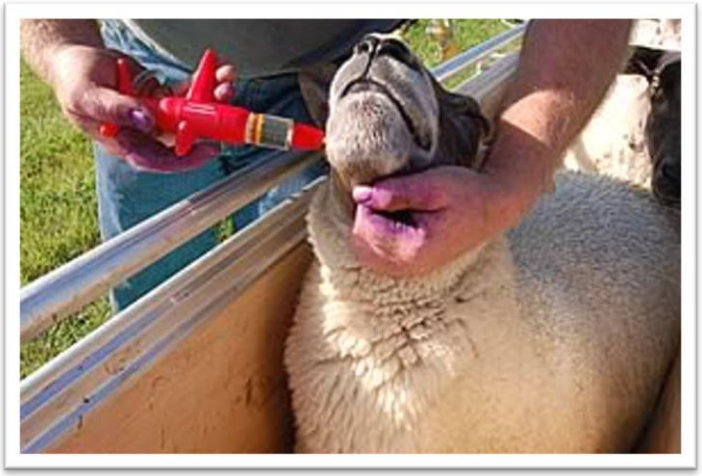


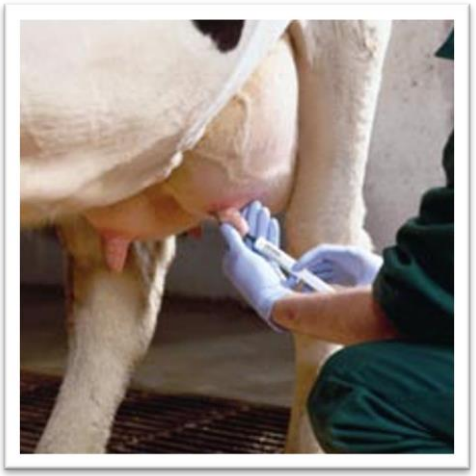
Pharmacokinetics - actions of body on the drug

How drugs get in and out……ADME

- absorption
- distribution
- metabolism
- excretion

Putting drugs in… routes of administration



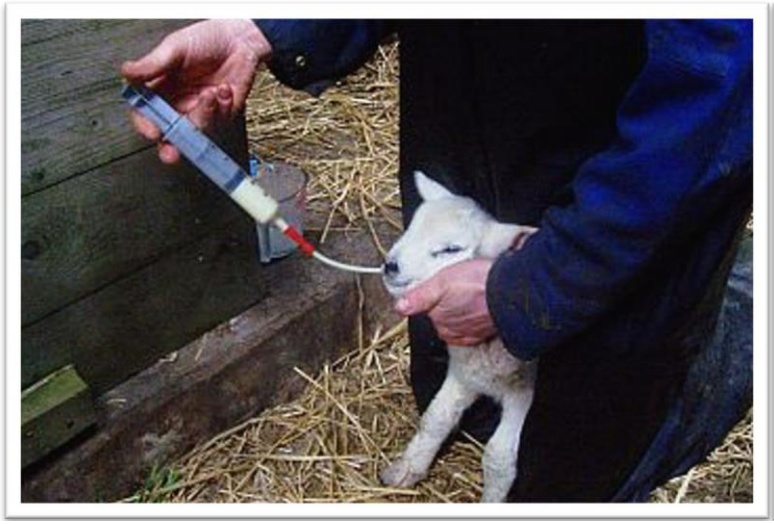


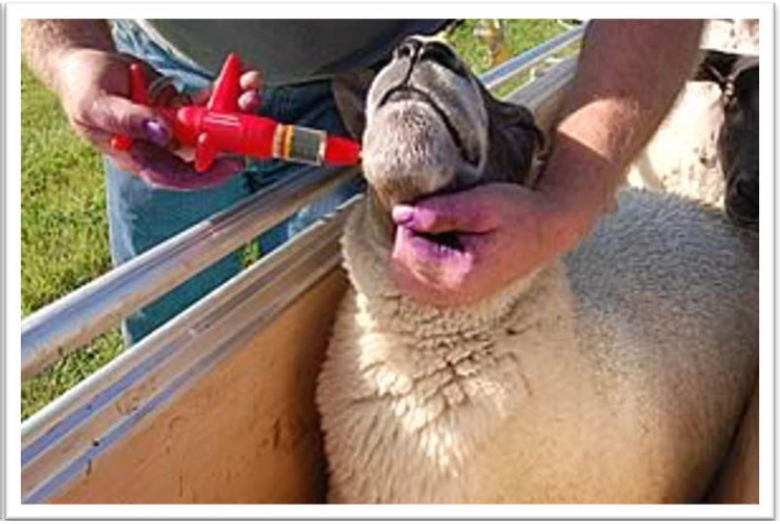
Drug administration

- There are two aspects to consider:
  - **Routes of administration: oral / parenteral / topical**
  - **Dose forms used**
- Several factors influence the choice:
  - Speed of onset required
  - Duration of action required
  - Site of action required
  - Ease of administration
  - Limitations imposed by the drug

Oral dose forms- liquid

- Mixtures, suspensions and linctuses
- Stomach tubes and drenches
- Licks (pasture and flank)
- Medicated water supply





Oral pastes

- Supplied in special syringes with doses marked on the plunger
- There are formulation issues:
  - Must not dry out
  - Need adhesive properties
  - Must be usable over wide temperature range
  - Need flavour and preservatives

Example: Felex Plus All Wormer Paste®

- Active ingredients are **niclosamide** and **pyrantel**
- Adhesion and the semi-solid formulation are achieved using **xanthene gum** and **silicone oil**
- There are preservatives and anti-oxidants
- Flavour is provided by adding **anchovy powder**

Parenteral administration

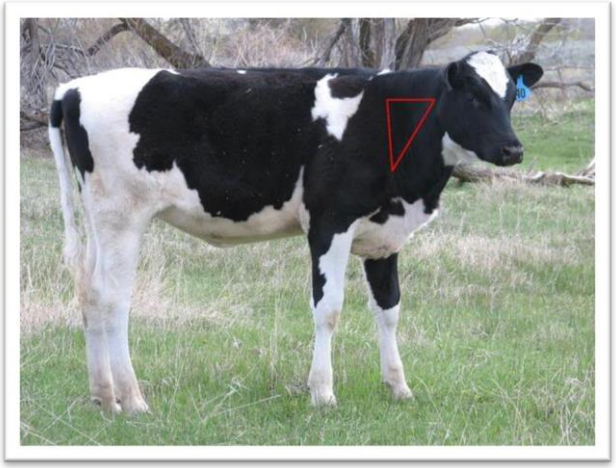
- Administration by **injection**
- Medicines for use by injection must be **sterile,** and preferably **isotonic** and **non-irritant**
- There is sometimes a limit to the **volume** which can be administered
- Routes of administration:
  - Intravenous (IV)
  - Intramuscular (IM)
  - Other (subcutaneous, intraperitoneal, intradermal, intra-lesional, intra-articular, intraruminal *etc*)

Intravenous administration

- Allows a **rapid onset** of drug action
- Also allows the administration of large volumes over a period of time
- It is easy for veterinary surgeons but probably not for their clients
- Medicines for IV use must be free of solid material and care must be taken to avoid the injection of air (emboli)

Intramuscular administration

- The onset of action is **slower than IV**
- It is possible to inject formulations containing solid material – to get a sustained release of drug
- Inadvertent IV administration is a slight risk
- Sometimes there is pain
- Damage to muscle tissue (ie meat/carcase)is a real risk



Intramuscular administration

- Damage to muscle tissue (ie meat/carcase)is a real risk

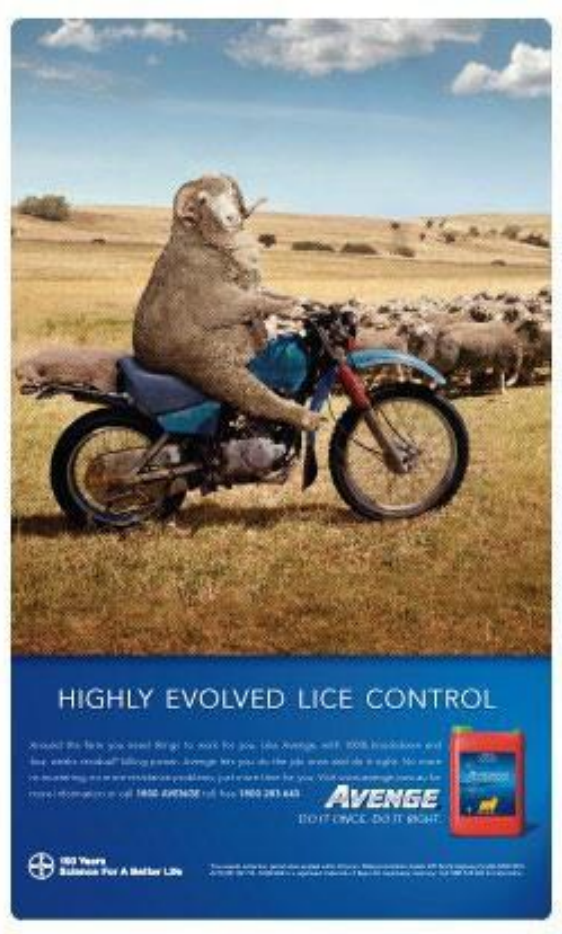
When administering an injection:

Give injections within the injection zone triangle, about 3 inches from the top of the neck. All SQ and IM injections must be administered in the triangle region ahead of the slope of the shoulder

Tent skin for all SQ injections, and space injections at least 4 inches apart.

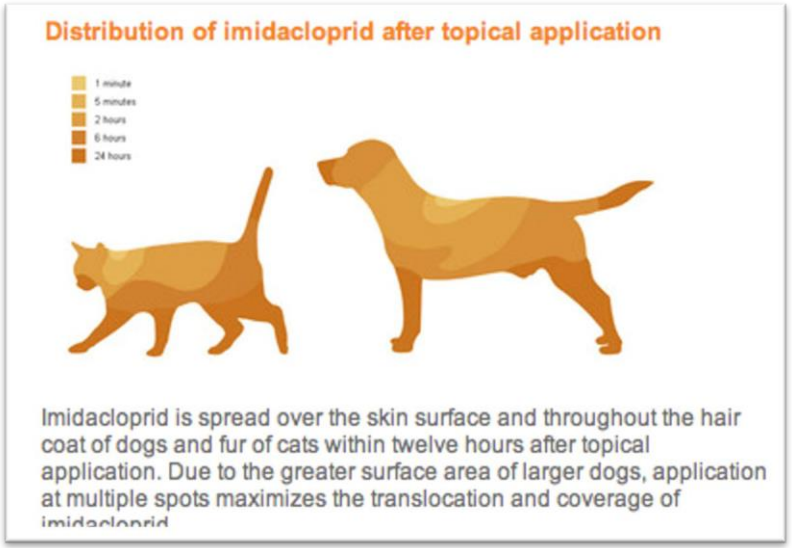
www.agrilabs.com

Topical administration



- **Transdermal:** The drug may be absorbed through the skin layers and circulate in the body (eg the -mectin group of anti parasitics)

- The drug may **disperse in the fat layer** on the skin surface (eg imidacloprid)



www.bayer.com

….other routes

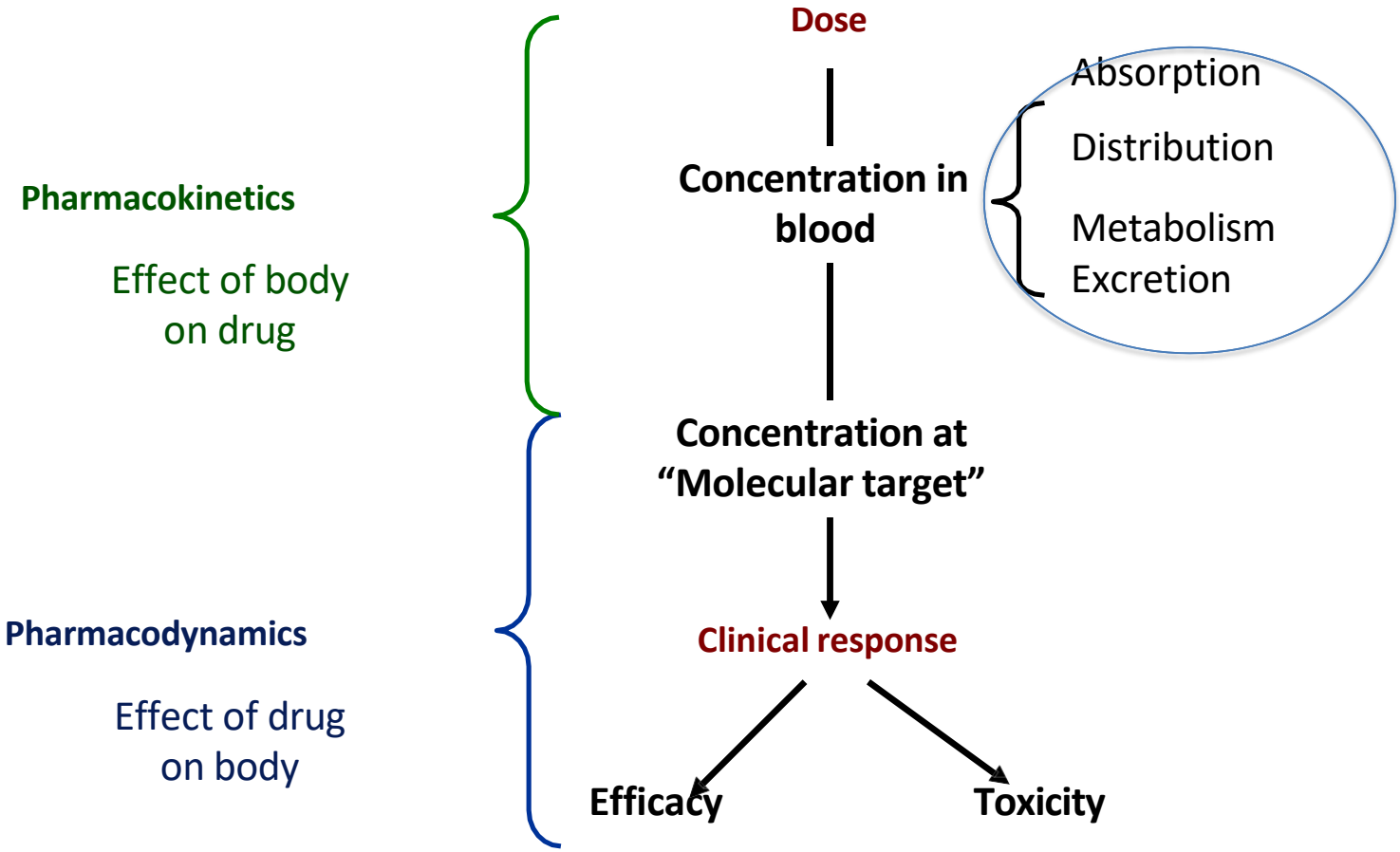
- Subcutaneous
  - Commonly used and safe
  - Less risk of carcase damage
  - Less painful

- Local administration

Local Administration

- Drug induces its effect at or near site of administration
- Access limited by absorption
- Drug excipient is designed to reduce absorption
- This can limit side effects
- Examples:
  - **Ocular:**
    - **Drops, ointments**
    - Regular washing by tears (therefore short acting)
    - Presence of enzymes ('hostile' environment)
  - **Intramammary**
    - May be short or long acting

Achieving the correct dose requires an understanding of pharmacokinetics



ABSORPTION

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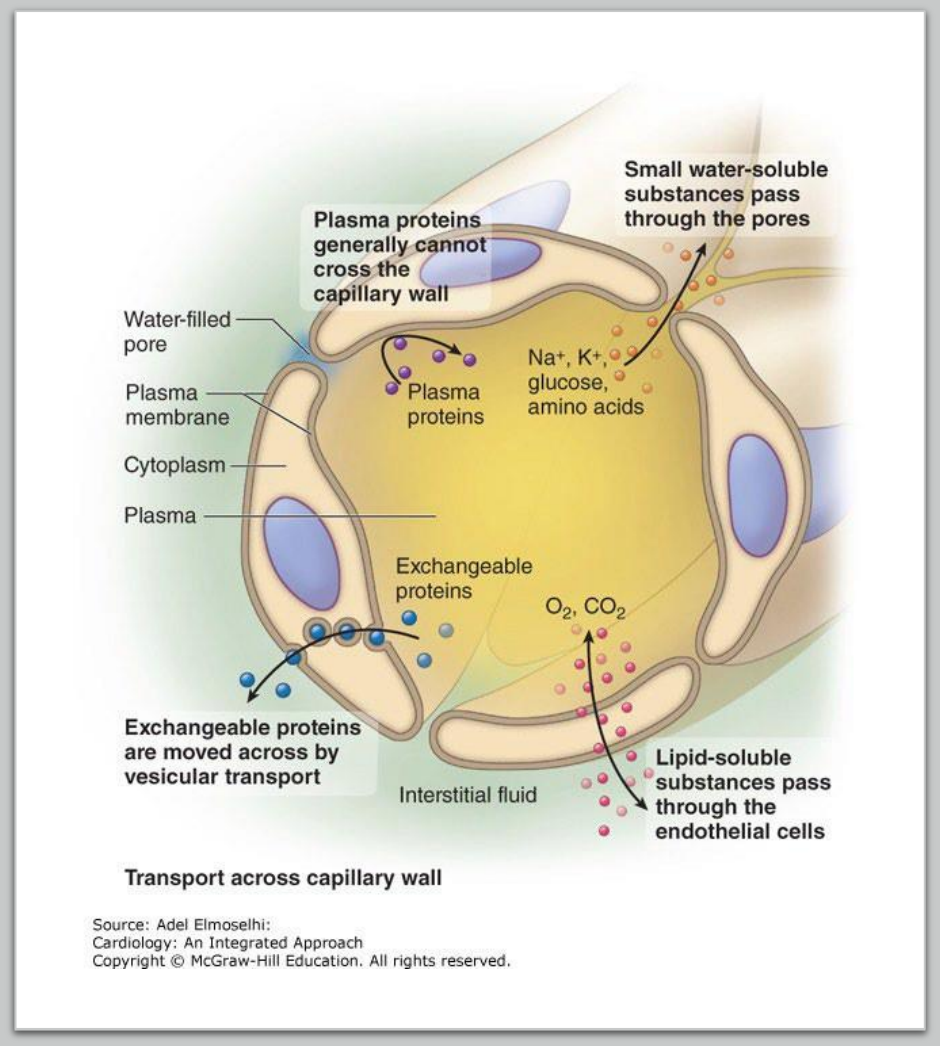
Movement of drugs across membranes

- Two methods of movement:
  - **Trans-cellular** (across the cells)
  - **Para-cellular** (between the cells)

- **Trans-cellula**r:
  - passive diffusion,
  - carrier-mediated transport
    - active transport
    - facilitated diffusion
  - Endocytosis

- **Para-cellular** - the movement of small drugs dissolved in water (‘**filtration’**)



Absorption through channels between cells: by Filtration

- Some water soluble drugs can pass **through** channels between cells, particularly hydrophilic and charged drugs
- There are **channels** of different sizes **between** the cells:
  - Capillaries – 5nm
  - Cells – 0.4nm
  - Blood-brain – no channel
- Actual size of the drugs will be influenced by the **water of hydration** (bigger and less likely to pass through the channels)
- Molecular weight cut-off for filtration is about 200 Da

Absorption across membranes: by Passive diffusion

- Most drugs pass **across** membranes by diffusion
- This is best if the drugs are **non-polar** (not charged, non-ionised, lipophilic)
- "A large non-polar molecule will cross a membrane far more readily than a small polar one"
- Drugs will pass down a **concentration** gradient (which is maintained by blood flow – acts as a 'sink')

Absorption across membranes: by **Active transport**

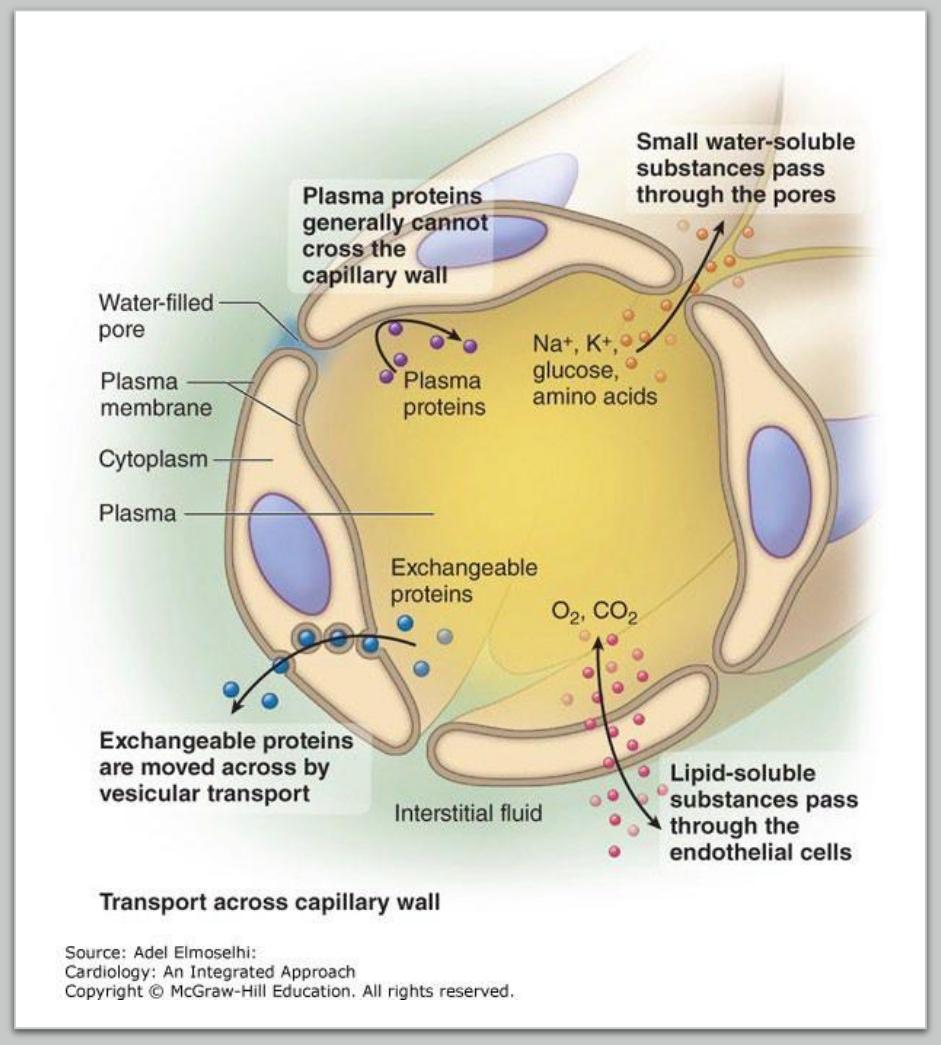
- Some drugs pass through membranes by carrier mediated transport
- This is a **selective** process which can be **saturated** ie the carrier is in limited supply and if excess drug is supplied it cannot be transported
- Several drugs may **compete** for one transport system
- Drugs can be transported **against** a concentration gradient
- Active transport requires **energy** and can be **inhibited**

Absorption: by Facilitated diffusion

- Movement of drugs across membranes can be by diffusion **assisted** by carrier molecules
- There is no net use of energy, the drug passes down a concentration gradient
- However, this sort of diffusion is selective and can be inhibited
- Facilitated diffusion takes place mostly in excretion

Absorption across membranes: by Endocytosis

- A small number of drugs are transported across epithelia by the cell membranes **enclosing** them within droplets (pinocytosis) or particles (phagocytosis)
- Receptors may play a role in the process
- Fat soluble vitamins, some vaccines and some macromolecules are transported this way



Drug absorption from the gastrointestinal tract

- **Oral drug administration** is convenient but often complex
- **Gut physiology** presents **barriers to absorption**
  - Gut enzymes in saliva, stomach and intestines (endogenous and from micro-organisms) can digest drugs
  - Gastrointestinal pH can denature **and** influence absorption
  - Food can bind to drugs, alter gut pH, alter gastric emptying etc
  - Disease states can change transit time, pH, absorptive capacity of the intestinal mucosa
  - Liver metabolism (first pass effect) can inactivate drug before it reaches systemic circulation

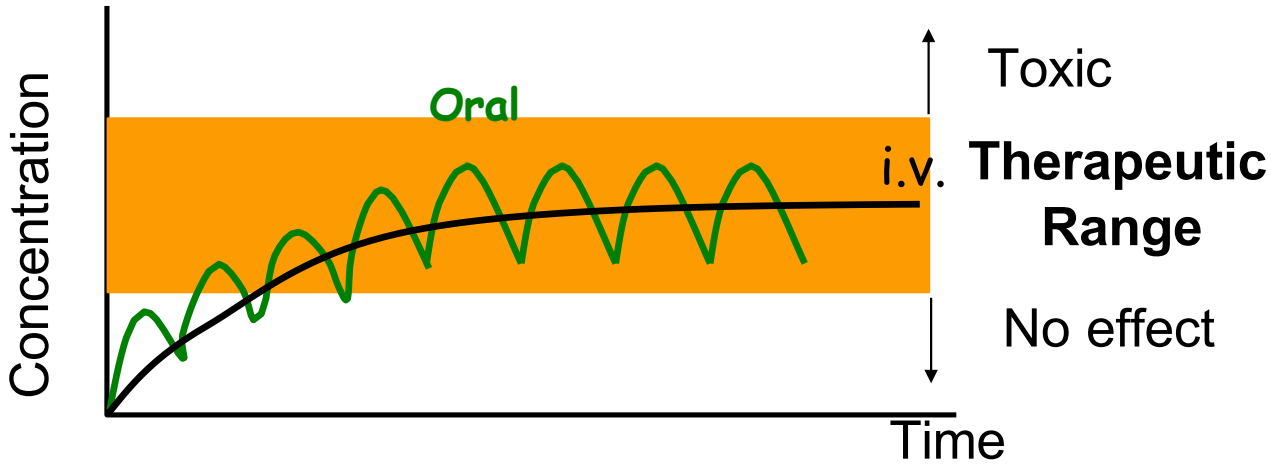
The concept of Bioavailability

- 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*)

The Kinetics of Oral Absorption
Staying in therapeutic range



When medication is given orally at intervals (eg tablets) the blood concentration varies over time

When a constant intravenous injection is given a “steady state” can be achieved- a plateau which occurs when drug administration equals drug elimination

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DISTRIBUTION

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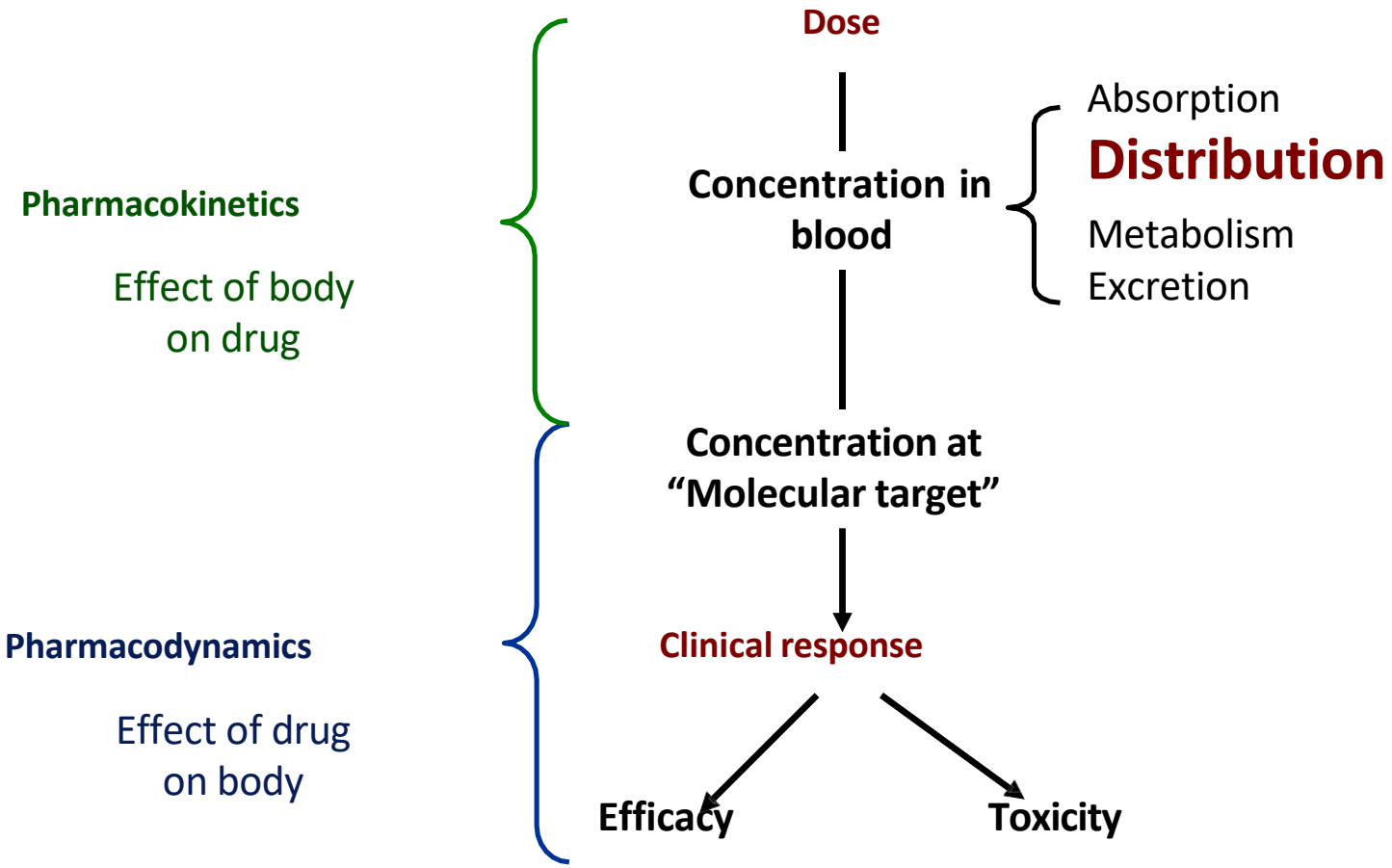
DISTRIBUTION



Distribution (ADME)

- Distribution is the transfer of drugs to sites of action, or storage,
- This usually occurs in the blood stream- ie is driven by circulation
- It generally occurs rapidly
- Several factors influence distribution:
  - Cardiac output
  - Tissue perfusion
  - Protein binding
  - Drug properties

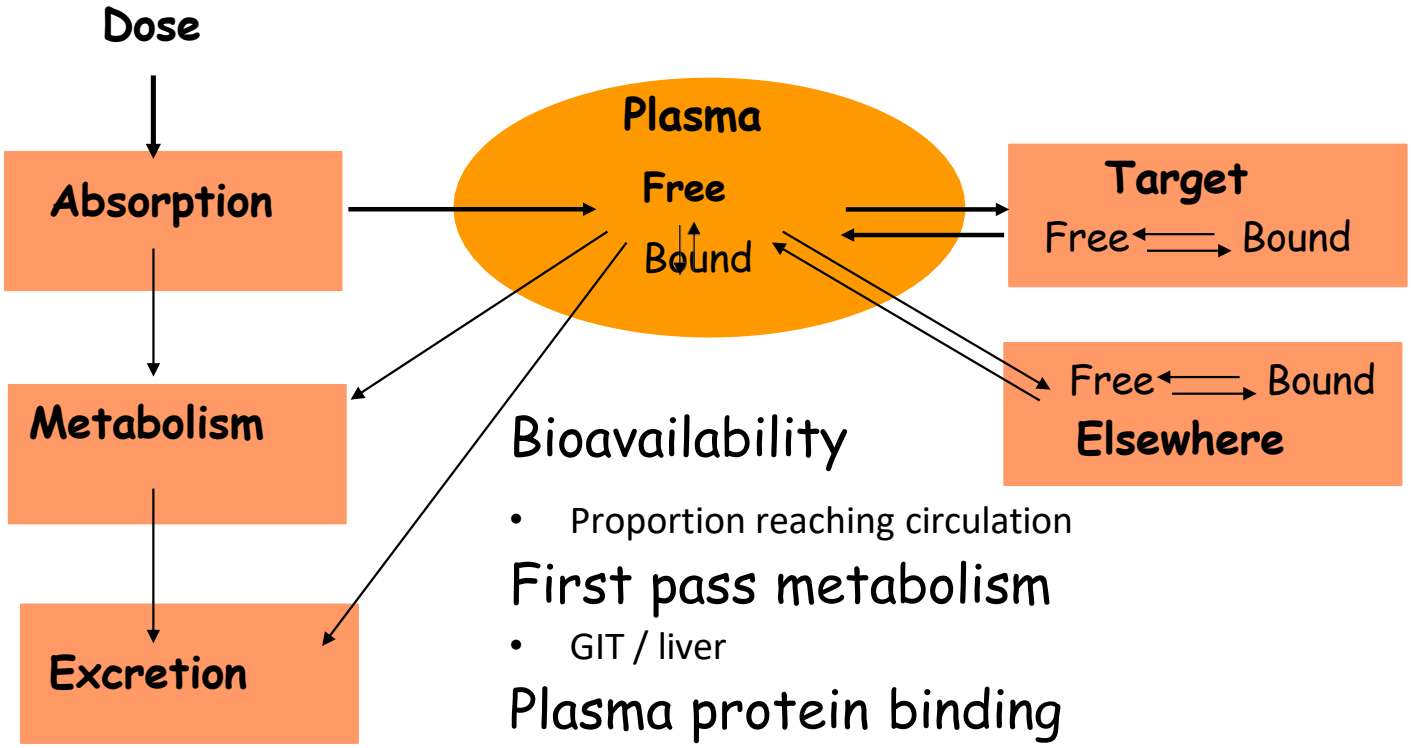
Steps of drug distribution

- Dilution in blood
- Movement into extracellular fluid
  - Only drugs that can “escape” the blood vessels
    - Small molecules
    - Not bound to plasma proteins
- Binding to cells/ uptake by cells
  - Requires specific receptor binding or
  - Lipid solubility

Pharmacokinetics- Distribution

What the body does to a drug

- processes influencing dose-concentration relationship



Bioavailability

- Proportion reaching circulation

First pass metabolism

- GIT / liver

Plasma protein binding

- Disease/ drug interactions

Protein binding

- Drugs can bind to serum proteins (albumin, alpha$_1$ glycoprotein and lipoproteins)
- This is a **quick** and **reversible** process
- The importance lies in the influence protein binding has on the **distribution** of drugs (**bound drug isn't filtered and isn't able to enter tissues)**
- One drug may **displace** another off proteins – to result in more free drug than expected

Factors affecting drug distribution

- Molecular size
  - Need to be small to cross vascular endothelium
- Ability to bind to plasma proteins
  - Unbound to cross vascular endothelium
- Lipid solubility
  - Need some lipid solubility to cross cell membrane
  - High lipid solubility will lead to sequestration in lipid

Objectives- Pharmacokinetics PART 1

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