Pharmacokinetics

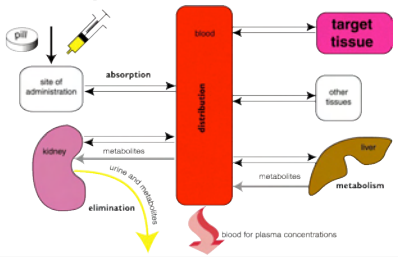
pharmacokinetics

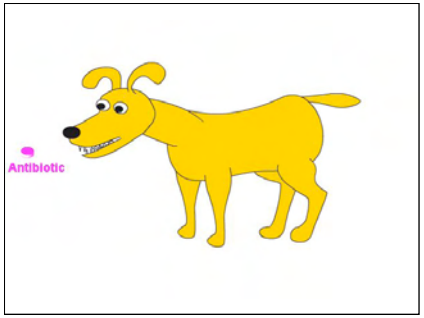
- What the animal does to the drug
- Movement of the drug in the body

pharmacokinetics

- absorption
- distribution
- metabolism
- elimination

pharmacokinetics





basic assumptions

- drugs must cross membranes to get to target
- actions are proportional to plasma concentrations

routes of administration

- enteral
  - via the gut
- parenteral
  - by injection
- other

routes of administration

- enteral
  - oral (po = *per os*)
  - sublingual
  - rectal

routes of administration

- parenteral
  - intravenous (iv)
  - intramuscular (im)
    - nb muscle becomes meat in food animals!
  - subcutaneous (sc or SQ)
  - intraperitoneal (ip)

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routes of administration

- inhalation
- topical
  - intramammary
  - intrauterine
  - onto cornea
- transdermal
- nasal
- epidural / intrathecal

absorption

- dissolution
- movement out of site of administration
- movement into blood vessels

dissolution

- most drugs must dissolve in water and oil
- ionisation important
  - pH important

dissolution

- main factors
  - pills
    - coatings
    - disintegrants
    - vehicle
  - all
    - solute

injection formulation

- solutions in water
  - rapid onset of action
- suspensions of insoluble salts
  - slower release
  - mixtures of salts can be used
  - not iv
- solutions in oil
  - slow release
  - not iv

injection formulation

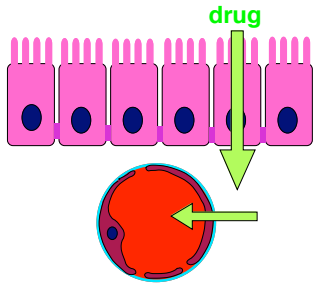
- complexes with soluble carriers
  - cyclodextrins
  - polyvinyl pyrrolidine (PVP)
  - propylene glycol
- used to get lipid soluble drugs into aqueous solution

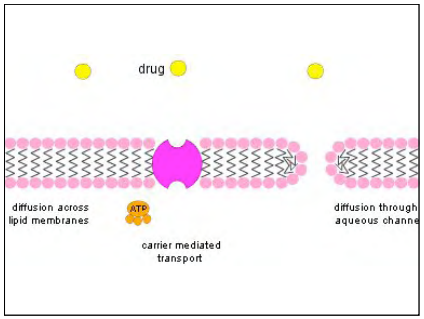
drug delivery devices

- “solution” in silicone rubber
  - very slow release
- osmotic pumps
  - predictable slow release
- mechanical pumps
  - variable rates of delivery
  - can be computer controlled ± feedback

barriers to absorption

- after iv administration
  - none
- after oral administration
  - gastric mucosa
  - endothelium
- after im or sc administration
  - endothelium



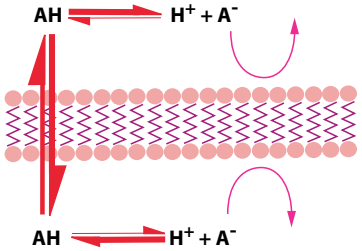


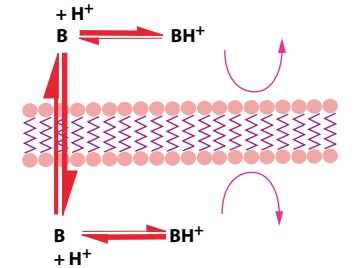
effects of pH

- most drugs are either weak bases or weak acids
- ionised forms are not lipid soluble

$HA \rightleftharpoons H^+ + A^-$

$BH^+ \rightleftharpoons H^+ + B$





Henderson Hasselbach equation

for acids $pH = pK_a + \log \frac{A}{AH}$

for bases $pH = pK_a + \log \frac{B}{BH^+}$

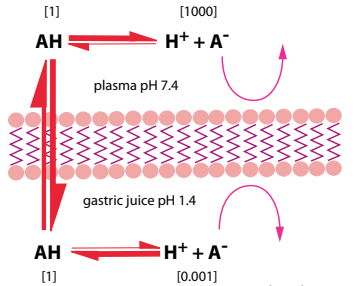
ie, when $pH = pK_a$, the drug is 50% ionised

effects of pH

- when pH < pKa, more protonated drug exists (AH & BH^+)
- when pH > pKa, more unprotonated drug exists (A^- & B)

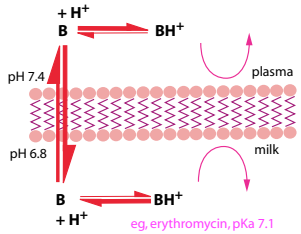
effects of pH

- bases are ionised in acid solutions
- acids are ionised in alkaline solutions



eg, aspirin - weak acid, pKa 4.4

ion trapping



eg, erythromycin, pKa 7.1

other factors influencing oral absorption

- blood flow
  - reduced in shock
- surface area
  - intestine > stomach
- contact time
  - reduced in vomiting & diarrhoea
- food
  - drugs may bind to food
- carrier mediated transport
  - both ways

other factors influencing parenteral absorption

- blood flow
  - im - medium speed
    - exercise
    - intra-fat rather than im!
  - sc - slow and variable
    - ambient temperature
- pH
- inflammation
- formulation

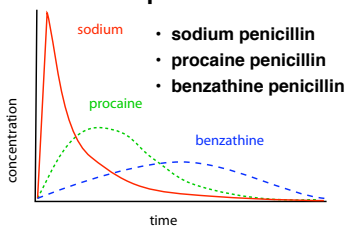
iv "absorption"

- absorption is bypassed by iv injection
- rate of injection = rate of absorption
- if rate of absorption is critical to the patient, iv infusion can be used

alterations in rate of absorption can have clinical effects

- antibiotics
- sedatives

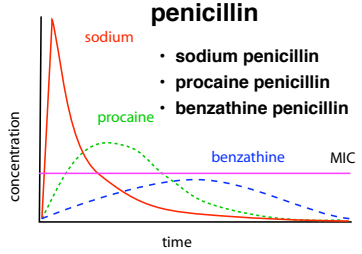
penicillin



- sodium penicillin
- procaine penicillin
- benzathine penicillin

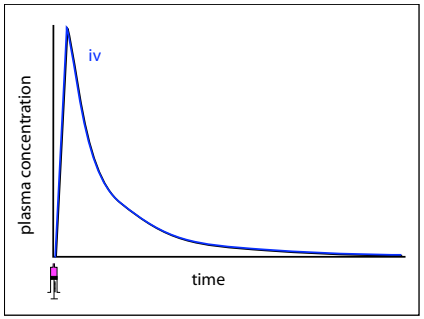
penicillin

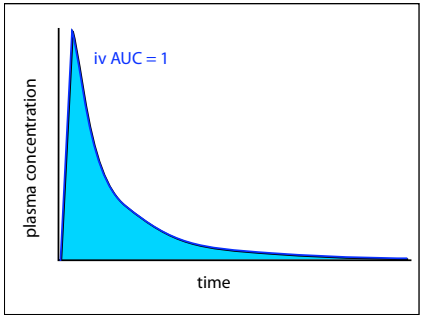
- **sodium penicillin**
- **procaine penicillin**
- **benzathine penicillin**

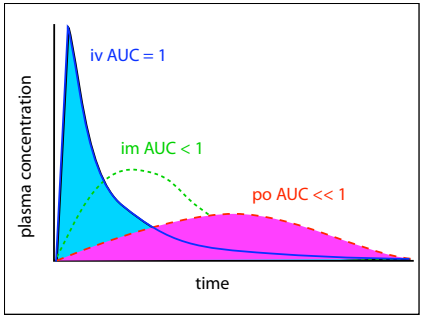


bioavailability

- **the fraction of a drug that reaches the systemic circulation**



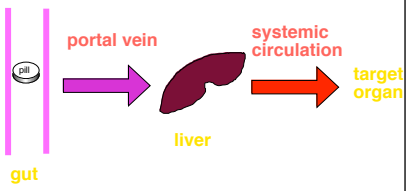




low bioavailability

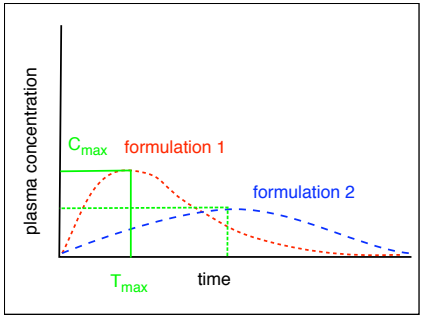
- poor absorption
  - very hydrophilic drug
  - chemical instability
  - drug formulation
- first pass metabolism

first pass metabolism



bioequivalence

- same bioavailability
- AUC
- peak concentration (C_{max})
- time to peak (T_{max})
- same effects



absorption

- **most drugs must be absorbed to act**
- **iv administration bypasses absorption**
- **absorption depends on lipid solubility and ionisation**
- **drugs are often formulated to provide delayed absorption**