Lec 7
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First order kinetics

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Michaelis - Menten reaction: most drugs

$$V = \text{rate of drug metabolism} = \frac{V_{max}[c]}{K_m + [c]}$$

catalysed by enzymes

$[c]$ = drug concentration
K_m = Michaelis - Menten constant

First order kinetics: $V = \frac{V_{max}[c]}{K_m}$

= metabolism is directly proportional to the concentration of free drug.

Zero-order kinetics = few drugs

$$V = \text{rate of drug metab.} = \frac{V_{max}[c]}{[c]} = V_{max}$$

- aspirin
- ethanol
- phenytoin

} dose very large

$[c]$ = greater than K_m

Mechanism:
- Enzyme saturation (high drug conc)
- Rate of metabolism constant (Non-linear kinetics)
- Constant amount of drug is metab
  Feed back inhibition. low metabolit

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Reactions of drug metabolism:

1- phase I reaction:-

a- lipophilic drug → polar molecules
- introducing
- unmasking } polar groups

e.g.
- OH
- NH_2

b- pharmacological activity =
- a- increased
- b- decreased
- c- unchanged.

c- cytochrom P450 enzyme system
- microsomal mixed function oxidases
- drug.
- endogenous substances (steroids, lipids)
- xenobiotics (= exogenous substan)
- sites = mainly liver, kidneys, intestine
- gene controlled
  - slow metabolize
  - fast metabolize
  - intermediate met.

d- inducers: drug interaction - phenobarb
- Rifampin

e- inhibitors:

Drug induction

- pharmakokinetic drug interaction.
- e.g. : phenobarbital
  : Rifampin
  : Carbamazepin
  : phenytoin
- increase Cytoch. p450 synthesis
- increase drug metabolism
- decrease drug plasma conc.
  e.g. warfarine
  phenytoin
  ibuprofen
  Tolbutamide
- decreased pharmacological effect.
- increased effect of active metabolites
- take times several weeks

Drug inhibition

- serious side effects.
- competitive inhibition - immediate effect
- example: : omeprazole
  cimetidin
  chloramphenicol
  erythromycin
  ketoconazole

drug	water
	grapefruit

- example = warfarin
  theophyllin
- increased plasma conc
- " pharmacological effect

phase I reactions not involving Cyt P450 system (5)

- catecholamine oxidation } amine oxidation
- histamine oxidation

- alcohol dehydrogenation → ethanol
- esterases = pravastatin metab.
- hydrolysis = procaine.

2- phase II reactions

- conjugation reaction:
  - glucuronic acid
  - sulfuric acid
  - acetic acid
  - amino acids

} large mol. more polar, water sol. inactive

NB: • Morphine-6-glucuronide → active
• Neonate are defient of glucuronidate (chloramphenicol)

• phase I → phase II
sequential

or direct

3. Reversal of order of the phase

isoniazid → acetylated (phase II) → hydroxylate (phase I)

Drug elimination

Definition: Removal of parent drugs or drug metabolites outside the body.

Routs:
- Renal } Renal failure - adjust dy
  Dialysis → remove drugs.
- bile } enterohepatic
- intestine } recycling
- lung - volatile anaesthetics.
- milk → Nursing mothers.

A- Renal elimination of drugs

1. glomerular filtration
2. Proximal tubular secretion
3. Distal tubular reabsorption

Glomerul filtration

- Renal artery
- glomerular capillary plexus
- capillary slits → free drug →

Bowman's capsule

- glomerular filtrate = 120ml/min
  (20% of renal plasma)
  = 600ml/min

- No effect of pH or lipid solubility of drugs on glomerular filtration.

Proximal tubules:

- efferent arterioles → capillary plexus
  → carries drugs that cannot filtrate into Bowman's capsule.
  1- active transport mechanism.
    - one for basic drugs
    - one for acidic drugs.

  2- energy requiring
    - carrier mediated
    - low specificity
    - competition among acids substances and among basic substances. (pharmacokinetic drug interaction)
      e.g. probenecid, penicillin G
      Aspirin - uric acid
    - premature infants neonates → incomplete development

Distal tubules

- drug concentration is higher than that in plexus surrounding tubules
- water soluble drugs, polar drugs } cannot reabsorbed
- lipid soluble drugs } reabsorbed.
- pH can influence ionization of weak acids or weak bases.

ionized forms → urine
unionized forms → increase drug clearance

examples: weak acid → alkalinization
(phenobarbital) (weak acid) (bicarbonate)

weak base → acidification
(cocain) (NH_4Cl)

drug poisoning → ionization
increase clearance