

Lect
OS
~~V/V~~
~~Q/H~~

First order kinetics

(2)

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

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

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

Zero - order kinetics = few drgs

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

- aspirin
 - ethanol
 - phenytoin
- } dose very large

$[c] = \text{greater than } K_m$

Mechanism: Enzyme saturation (high drug conc)

- rate of metabolism constant

(Non-linear kinetics)

- Constant amount of drug is metabolized back inhibition in metabolism

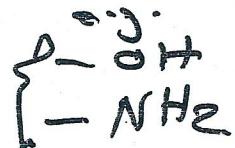
(1)

Reactions of drug metabolism:

(3)

1- phase I reactions:-

- a- lipophilic drug \rightarrow polar molecules
 - introducing } polar groups
 - removing } groups



b- pharmacological activity =

- a- increased
- b- decreased
- c- unchanged.

c- cytochrome P₄₅₀ enzyme system

- microsomal mixed function oxidases
- drug.
- endogenous substances (steroids, lipids)
- xenobiotics (exogenous substances)
- sites = mainly liver, kidneys, intestine
- gene controlled
 - slow metabolism
 - fast metabolism
 - intermediate rate

d- inducers! drug interaction - phenobarbital

- Rifampin

e- inhibitors!

(D)

Drug induction

(4)

- pharmacokinetic drug interaction.
 - e.g.: phenobarbital
 - Rifampin
 - Carbamazepine
 - phenytoin
- increase Cytoch. p450 synthesis
- increase drug metabolism
- decrease drug plasma conc.
 - e.g.: warfarin
 - 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
- | | | | |
|------|--------------|-----------------|------------|
| long | cimetidine | chloramphenicol | water |
| = | erythromycin | ketocconazole | grapefruit |
- example = warfarin
- heparin
- increased plasma conc
- increased pharmacological effect

(3)

phase I reactions not involving Cyt P450 system

- catecholamine oxidation { amine oxidation
- histamine oxidation
- alcohol dehydrogenation \rightarrow ethanol
- esterases = pravastatin metab.
- hydrolysis = procaine.

2- phase II reactions

- conjugation reaction:
 - glucuronic acid } glycol mol.
 - sulfuric acid } more polar
 - acetic acid } water sol.
 - amino acids } inactive

NB: Morphine - 6 - glucuronide \rightarrow active
• Neonatal enzymes efficient of glucuronidation
(chloramphenicol)

• phase I \rightarrow phase II

sequential

or direct

3. Reversal of order of the phases

isoniazide \rightarrow acetylated \rightarrow hydroxylated
(phase II) (phase I)

Ding elimination

(6)

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

Routs :

Renal	{ Renal failure - adjust dg Dialysis → remove drgs.
bile	{ enterohepatic
intestine	recycling
Lung - volatile anaesthesia.	
milk → Nursing mothers.	

A- Renal elimination of drug

1. glomerular filtration

2. Proximal tubular secretion

3. Distal tubular reabsorption

(5)

Glomerular filtration

②

- Renal artery
- glomerular capillary plexus
- capillary slits \rightarrow freely drug \rightarrow

Bowman's capsule

- glomerular filtrate = ~~200ml/min~~
- (20% of renal plasma)
 $= 600 \text{ ml/min}$

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

(b)

Proximal tubules:

(3)

- effluent arterioles → capillaries of glomeruli
- carries drugs that can't 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
substances.)

drug interaction

e.) propranolol, penicillin G

Aspirin - uric acid

- premature infants

- re-nates → incomplete
development

(4)

Distal tubules

②

- drug concentration is higher than that in plasma surrounding tubules
- water soluble drugs } can't reabsorb
polar drugs } reabsorbed
- lipid soluble drugs } reabsorbed
- pH can influence ionization
weak acids or weak bases.

ion trapping \rightarrow urine
for ionized forms \rightarrow increase drug clearance

examples of weak acid \rightarrow alkalinization

(phenobarbital) (bicarbonate)
(weak acid)

\Rightarrow weak base \rightarrow acidification
(cocaine) (NH_4Cl)

drug molecule \rightarrow ionization
increase clearance