Drug metabolism:

Definition:

irreversible biotransformation of drugs:-

Organs = mainly liver.

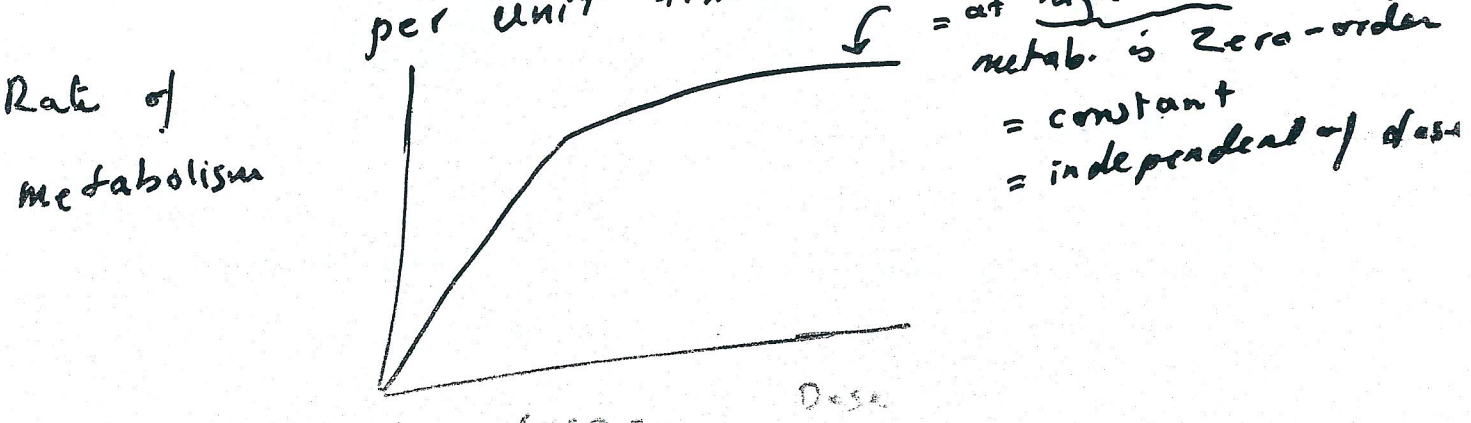
Metabolites = mainly bile or urine.

- active metabolites
- inactive "

Kinetics of metabolism

A - First order kinetics

- Catalyst = Enzyme
- order = Michaelis Menten kinetics:
- rate of drug metabolism is directly proportional to the concentration of free drug.
- First-order kinetics = constant fraction of drug is metabolized per unit time.



- Low dose:
- first-order metabolism
- = proportional to drug dose.

B- Zero-order kinetics

= Few drugs

- aspirin
- Ethanol
- phenytoin
- Large doses of other drugs.

First order

= Velocity Equation :

v = rate of drug met. =

$$\frac{V_{max}[C]}{K_m + [C]}$$

v = rate of drug metab =

$$\frac{V_{max}[C]}{K_m}$$

[C] = much less than Km

= Constant fraction of drug is metabolized per unit time

Zero-order

velocity Equation :

v = rate of drug metab. =

$$\frac{V_{max}[C]}{[C]} = V_{max}$$

= [C] = much greater than Km

Enzyme saturation by high free-drug conc.

= metab. rate = remain constant over time

= Non-linear kinet.

= Constant amount of drug is metab per unit time

Reactions of drug metabolism :

Lipophilic drugs
(lipid soluble drug)

Circulating drug → Kidney → filtration → Reabsorption → Circulating drug

Circulating drugs → liver → biotransformation
↓
lipophilic drug (metabolites)
↓
kidney
↓
filtration
↓
No reabsorption
↓
urine

Hepatic Biotransformation

1- phase 1 = Non-polar drugs → more polar drugs

catalyst = Cyt p450 system
microsomal mixed function Enzymes

oxidation =

2- phase II = Conjugation reaction + Endogenous substances

glucuronate
suphate
Acetate etc.

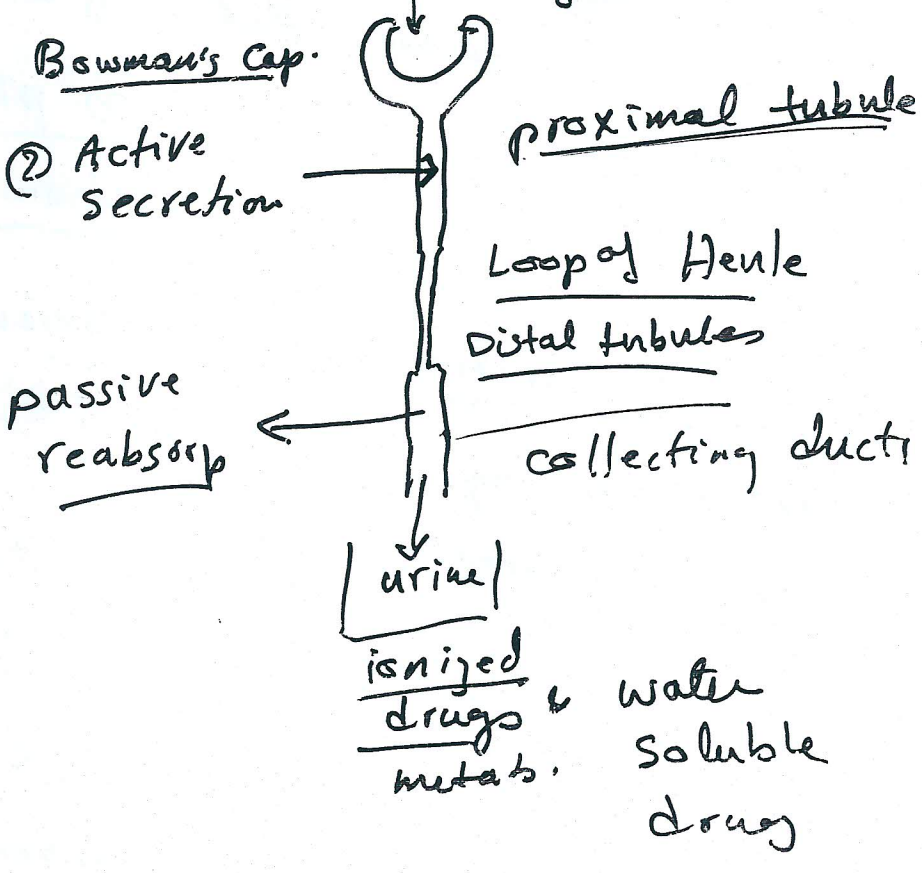
Drug Elimination

organs of elimination

- Main = kidney = most important
  ↓
  urine
- others =
  - liver → bile
  - intestine
  - lung
  - Breast → milk

Renal Elimination

① filtration — only free drugs enter glomerular filtration



Glomerular filtration

1- Renal arteries → glomerular capillary plexus.

Blood → plasma

↓ free drug

↓ capillary slits

↓ Bowman's caps space

↓ glomerular filtrate

= (125 ml /min) = 180 L/day

= No effect of 1) drug lipid solubility

2) pH has no effect.

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proximal tubular secretion:

active drug secretion: → ① anions (A⁻) → a) deprotonated of weak acids

- energy requiring
- Carrier mediated

② Cations → protonated weak base (BH^+)

- Low specificity = many comp.
- Competition between drugs (Drug interaction)

→ premature infants, Neonates immature system

↓ retain certain drugs.

Distal tubular reabsorption:

① - Drug concentration exceeds of that in the perivascular sp

② - uncharged drugs reabsorbed from nephric lumen bac into the systemic circulation (passive diffusion)

③ pH of nephric fluid can influence the drug ionization form

④ pH manipulation can influence drug reabsorption or trapping. (ionization)

↓

increase reabsorp.
↓ elimination

↓

- increase drug eliminatio
- ↑ drug clearance

e.g.: phenobarbital overdose (acidic drug) + bicarbonate

↓

urine alkalinizatio

↓

more ionized phenobarbital

↓

↓ reabsorption

weak base drug

+ NH_4Cl

↓

acidification of urine

↓

protonation of drug (BH^+)

↓

↑ clearance

(ion trapping)