Drug Elimination & Excretion

Dr. Shaikh Fahad Falah

Drug elimination

- “to put an end to the pharmacological actions of a drug through inactivation or removal of active drug from the body by excretion is called elimination”

- Elimination of drug is achieved either by drug metabolism or excretion, or by both mechanisms.
- Elimination of a drug from the body may involve processes occurring in kidneys, lungs, liver and other organs.
- The rate of elimination determines the duration of action for most drugs

- Drugs which forms active metabolites e.g. **diazepam,** elimination of parent drug molecule by metabolism, does not mean termination of pharmacological action of drug.

- Some drugs combines irreversibly to their receptors, so disappearance from blood stream does not mean its cessation of action occurs e.g. **phenoxybenzamine**, an irreversible inhibitor of α adrenoceptors is eliminated from plasma in less than an hour after administration but its action lasts for 48 hrs.

Drugs show two types of kinetics of drug elimination

- First-order elimination
- Zero-order elimination

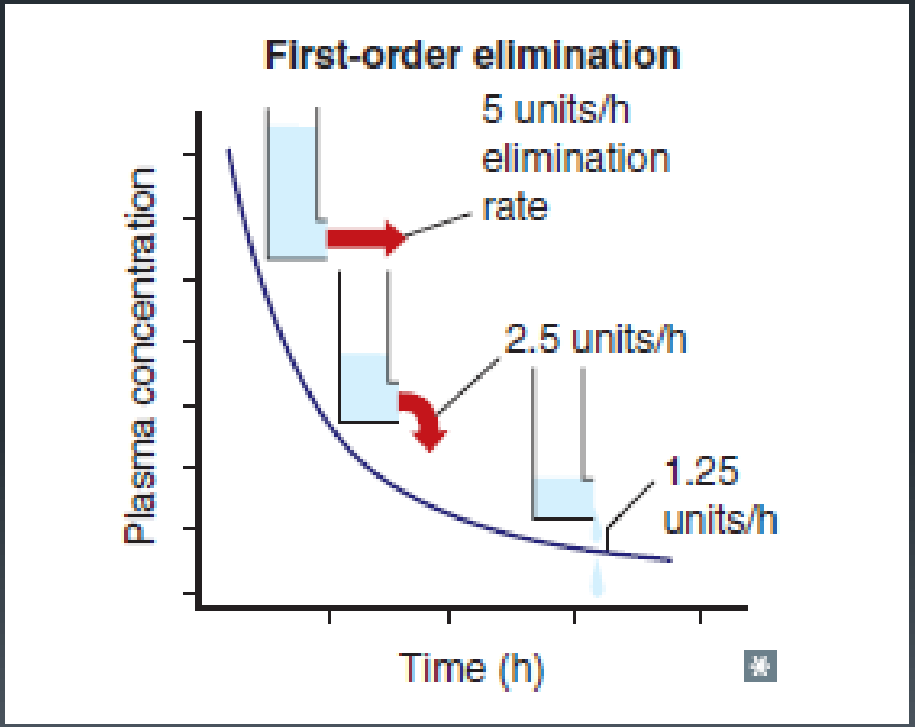
First-order elimination

- It implies that rate of elimination is proportional to the concentration of drug in plasma i.e.

  higher the concentration, greater the amount of drug eliminated per unit time.

- Drugs with first order elimination their half-life is constant.

First-order elimination

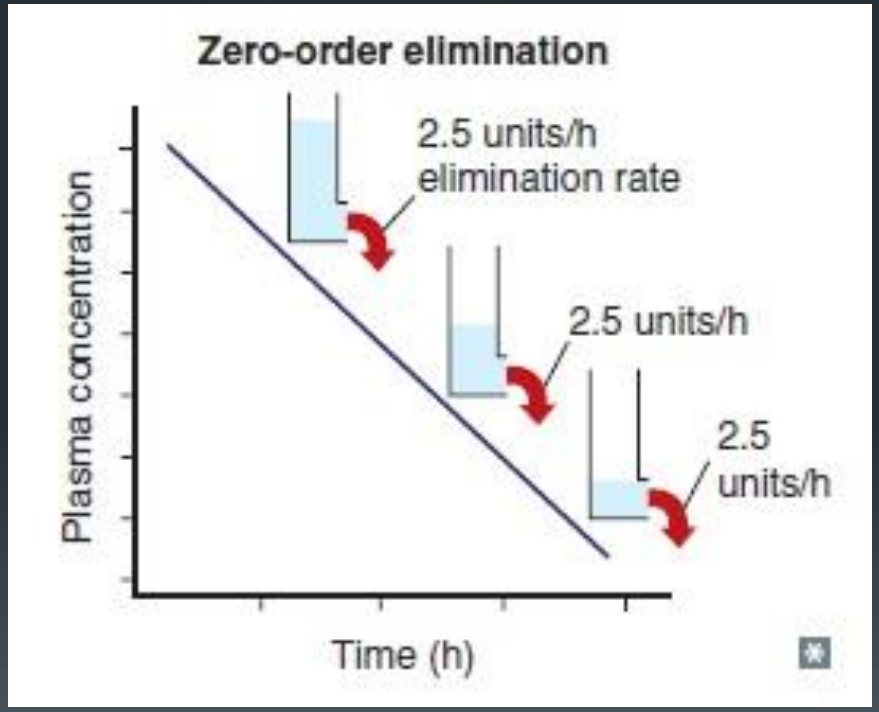


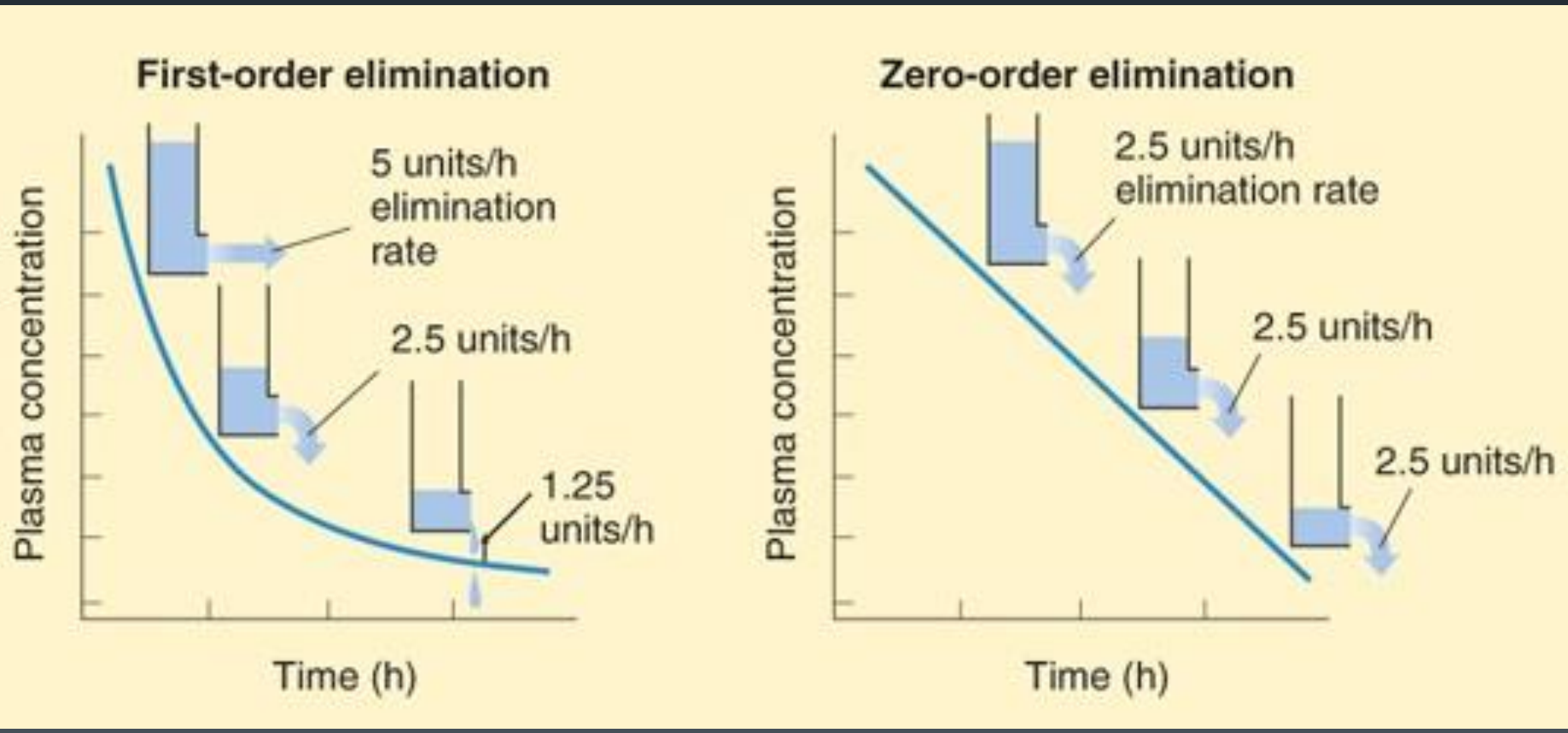
Zero-order elimination

- It implies that rate of elimination of drug is constant regardless of its concentration in the body.
- A constant amount of drug is metabolized per unit time, irrespective of plasma concentration.
- It is also known as capacity-limited, or Michaelis-Menten elimination.

- **Alcohol** shows first-order kinetics at plasma conc. 10/100ml, when plasma concentration is raised it show zero-order kinetics because of limited availability of the cofactor NAD+ alcohol dehydrogenase.
- At higher doses **phenytoin** show zero order kinetics.
- **Aspirin** at toxic doses shows zero-order kinetics.
- These drugs show zero-order kinetics due to saturation of enzymes or exhaustion of endogenous reactants or cofactors of enzymes.

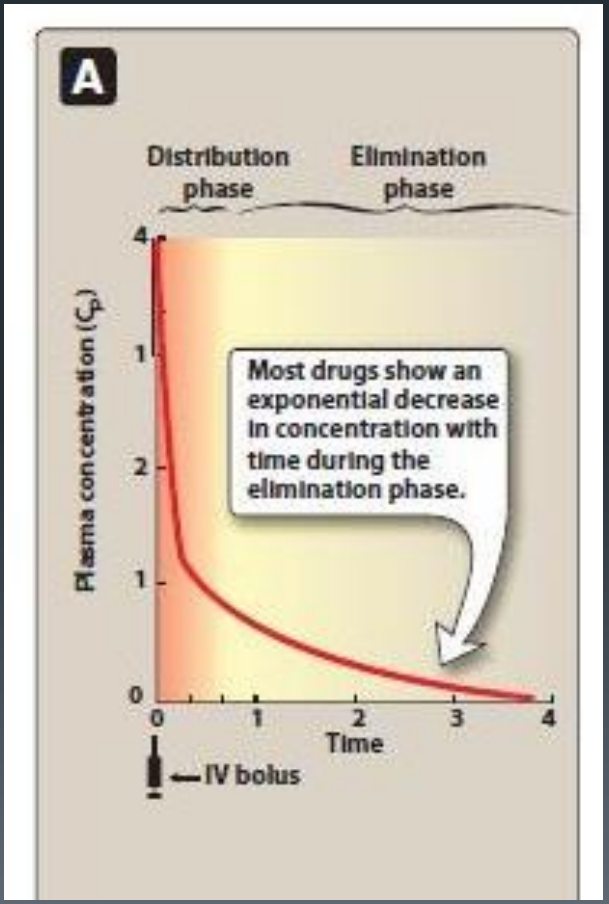
Zero-order elimination

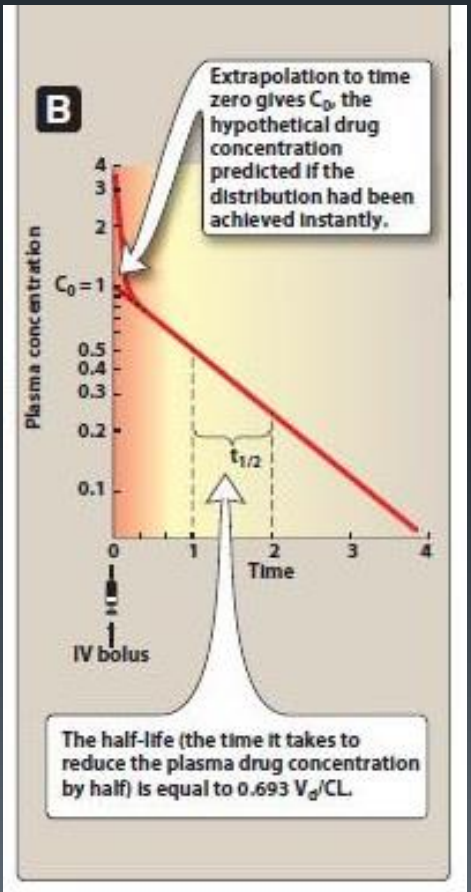



First-order elimination
Plasma concentration
5 units/h
elimination
rate
2.5 units/h
1.25
units/h
Time (h)
Zero-order elimination
Plasma concentration
2.5 units/h
elimination rate
2.5 units/h
2.5 units/h
Time (h)

Plasma half life of drugs

- Half life of a drug is the time taken for the drug to fall to half of the observed/initial concentration.





- For example:

if the initial concentration of a drug is 100 mg/ml and concentration becomes 50 mg/ml in 5 hour.

Then its half life is 5 hours.

$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$

Where:

$T_{1/2}$= half life

V_d= volume of distribution

CL= clearance

(0.7 = constant)

Half life of a drug is increased by:

- Decreased renal or hepatic blood flow. E.g. in shock & heart failure.
- Decrease in extraction ratio e.g. renal disease, cirrhosis liver
- Decreased drug metabolism e.g. enzyme inhibition by co-administered drug or by cirrhosis liver.

Half life of a drug is decreased by:

- Increased hepatic blood flow.
- Decreased plasma protein binding. Free fraction of drug is increased which is subjected to metabolism.
- Increased drug metabolism e.g. enzyme induction.

Clinical significance:

- Half life Helps in adjustment of dose and especially to determine the time interval b/w doses. i.e. *dosing* schedule.
- It Indicates how quickly a drug is removed from plasma by biotransformation or excretion, therefore helps to estimate the time that is important for a patient who has got overdose or *poisoning* by any drug.
- It determines mode of administration for some drugs e.g. ultra-short acting drugs must be given by *I/V infusion* like sodium nitroprusside.
- It Helps in determination of *steady-state concentration* of drug.
- It Helps in calculation of *loading dose, & maintenance dose* of drugs.

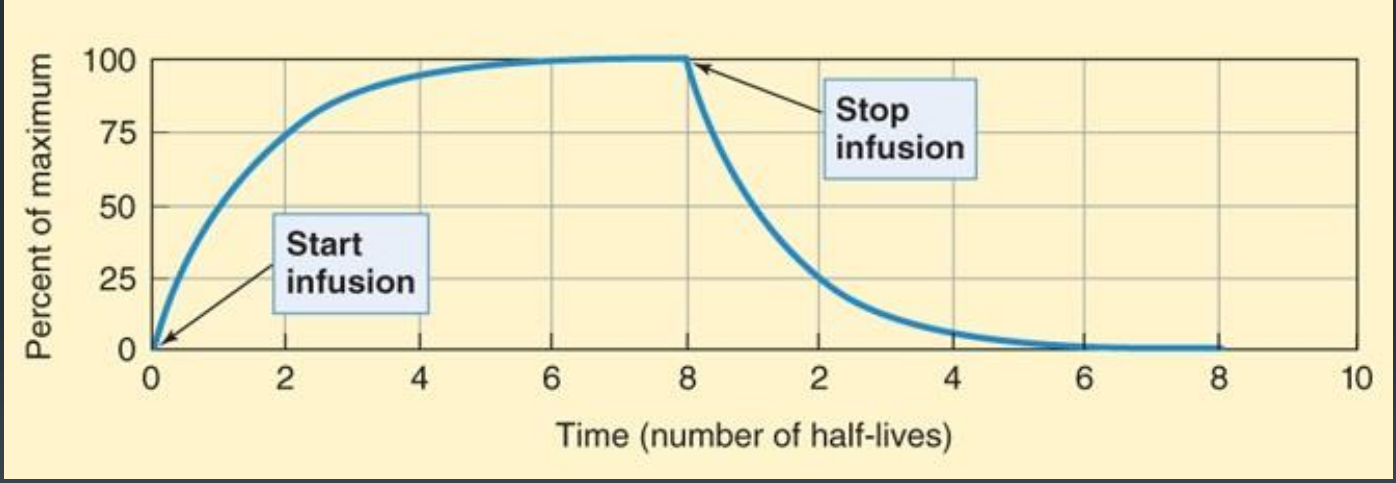
Steady state concentration

- When a drug is administered , the concentration of drug in plasma rises, until a level/state is reached where the concentration become constant, even if the administration of drug continues. This state is called steady state & the concentration in the plasma is called steady state concentration of drug.

- At steady state the rate of drug infusion is equal to rate of its elimination.

- When a drug is given through an I/V infusion, the conc. Of drug in plasma rises until the rate of drug elimination becomes precisely equal to the rate of drug administration.
- Concentration of drug reaches 50% of steady state after half life, 75% after second, 87.5% after 3rd half life.
- It is assumed that steady state of a drug is reached in about four half lives.
- Quick attainment of the steady state can be achieved by starting with a larger dose, called the loading dose.

Steady state concentration



Clearance:

- The volume of plasma from which all the drug appears to be removed in a given time.

OR

- The ratio of rate of elimination of a drug to its concentration in plasma.

$$CL = \frac{\text{Rate of elimination}}{C}$$

Where:

CL= clearance of drug

C= Plasma drug concentration

- $CL_{(renal)} = \frac{\text{rate of elimination}_{(kidney)}}{C}$
- $CL_{(liver)} = \frac{\text{rate of elimination}_{(liver)}}{C}$
- $CL_{(other)} = \frac{\text{rate of elimination}_{(other)}}{C}$
- $CL\ systemic = CL\ renal + CL\ liver + CL\ other$

Factors affecting clearance:

- Blood flow to organ of clearance, especially for drug whose clearance is flow-limited.
- Extraction capacity of organ of clearance.
- Condition of organ of clearance i.e. any disease of that organ.
- Plasma protein binding i.e. if plasma protein concentration is decreased than free fraction of drug will be rapidly cleared.

Excretion of drugs

- Excretion is the process by which drugs or metabolites of drugs are transferred from the body to external environment.

- TYPES OF EXCRETION
  - 1. RENAL EXCRETION
  - 2. NON RENAL EXCRETION
    - Biliary excretion.
    - Pulmonary excretion.
    - Salivary excretion.
    - Mammary excretion.
    - Skin / Dermal excretion.
    - Gastrointestinal excretion.

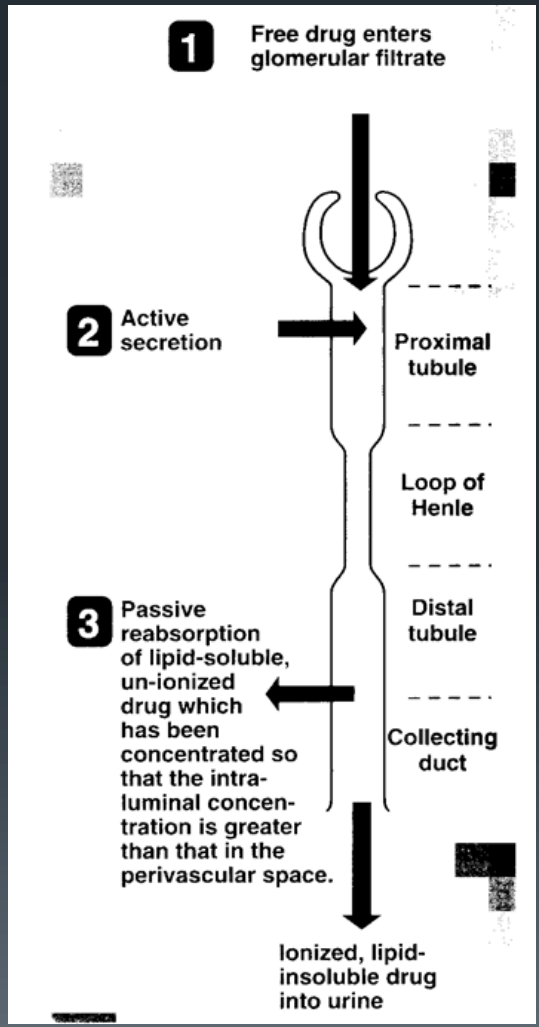
Processes involved in renal excretion:

- **Glomerular filtration:**

  under high hydrostatic pressure most drugs, not bound to plasma proteins , are freely filtered into bowman's capsule as a part of glomerular filtrate.

- Drug transport is dependent on
  - Size - MW cut off = 5000

    > 75,000 – restricted
  - Charge - charged substances are filtered slower
  - Shape – globular proteins are filtered slower
  - Lipid soluble drugs – also by passive diffusion

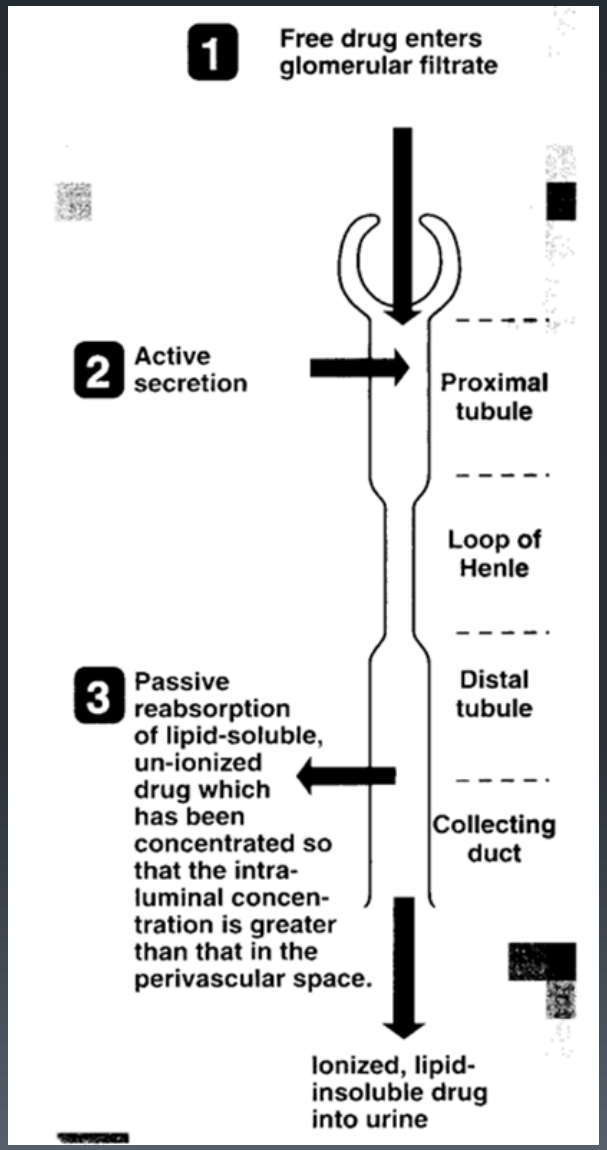


- **Active tubular secretion:**

  is the process of active transport-mediated excretion of charged drugs by proximal renal tubules.

- Relatively non-specific
- Anion/acid system – penicillins, phenobarbital, uric acid, etc.
- Cation/base system – morphine, catecholamines, histamine, etc.

- In some cases can remove protein-bound drugs from the blood
- Possess all the characteristics of active transport e.g. saturation, energy requirement, competition, unidirectional.

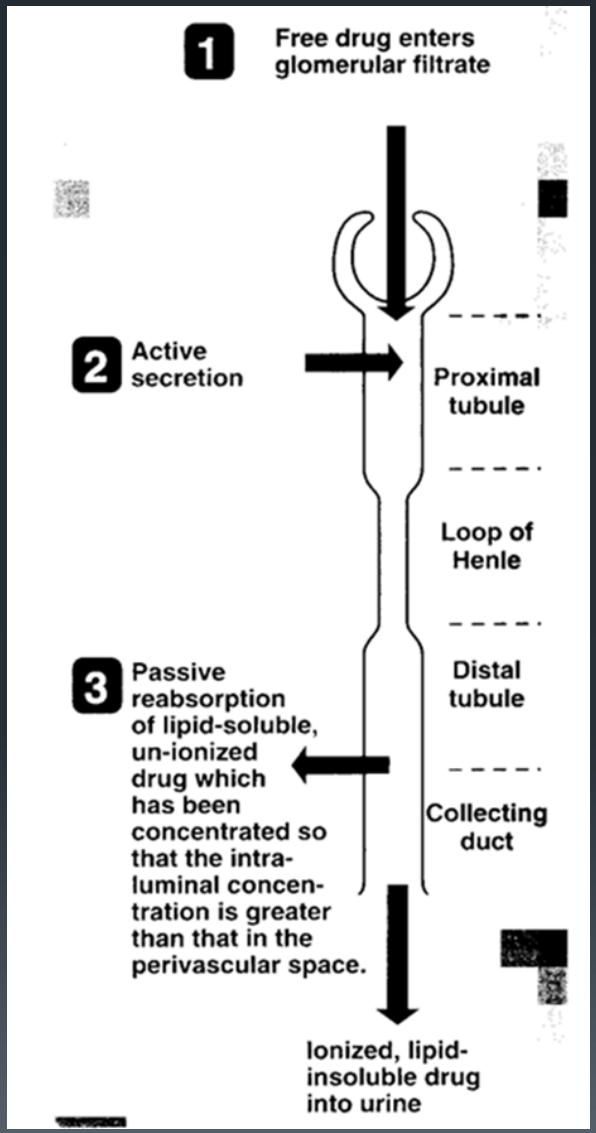


- **Passive tubular reabsorption:**

it means reabsorption of filtered drug back into the circulation along the concentration gradient of the drug

- Transfer of unionized, lipid soluble drugs back to the blood by diffusion – passive reabsorption
- Excretion of ionized, lipid-insoluble drugs
- More ionization – more secretion

- Acidification of urine causes reabsorption of weak acids - Ammonium chloride or ascorbic acid– decrease pH – enhance excretion - forced acid diuresis
- Forced alkaline diuresis - Bicarbonate – increase pH – ionization of weak acids – faster excretion



Excretion through liver:

- Drugs are filtered from liver capillaries into interstitial fluid – liver has larger fenestrae which will allow the filtration of most drugs
- Drugs in interstitial fluid are transported into hepatocytes by
  - Passive diffusion
  - Carrier-mediated transport
- Lipid insoluble or ionized drugs – excreted
- Enterohepatic cycling: Liver → Bile → intestine

  - Lipid soluble – reabsorption from intestine to bile – transport back to the liver
  - Conserve endogenous substances – VD3, B12, folic acid, estrogens.
  - This process results in prolongation of half lives of drugs. Some drugs undergoing enterohepatic cycling are cardiac glycosides, rifampicin and chlorpromazine.

- PULMONARY EXCRETION:

- Gaseous and volatile substances such as general anesthetics (Halothane) are absorbed through lungs by simple diffusion.
- Pulmonary blood flow, rate of respiration and solubility of substance effect PE.
- Intact gaseous drugs are excreted but not metabolites.
- Alcohol which has high solubility in blood and tissues are excreted slowly by lungs

- SALIVARY EXCRETION :

- Unionized lipid soluble drugs are excreted passively.
- The bitter after taste in the mouth of a patient is indication of drug excreted.
- Some basic drugs inhibit saliva secretion and are responsible for mouth dryness.
- Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline .

- MAMMARY EXCRETION:

- Milk consists of lactic secretions which is rich in fats and proteins.
- Excretion of drug in milk is important as it gains entry in breast feeding infants.
- Free un-ionized and lipid soluble drugs diffuse passively.
- Highly plasma bound drug like Diazepam is less secreted in milk.
- Amount of drug excreted in milk is less than 1% and fraction consumed by infant is too less to produce toxic effects.
- Some potent drugs like barbiturates and morphine may induce toxicity.
- Discoloration of teeth with tetracycline and jaundice due to interaction of bilirubin with sulfonamides.
- Nicotine is also secreted in the milk of mothers who smoke

- SKIN EXCRETION :

- Excretion of drugs through skin may lead to urticaria and dermatitis.
- Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

- GASTROINTESTINAL EXCRETION:

- Excretion of drugs through GIT usually occurs after parenteral administration.
- Water soluble and ionized form of weakly acidic and basic drugs are excreted in GIT.
- Example are nicotine and quinine are excreted in stomach.
- Drugs excreted in GIT are reabsorbed into systemic circulation & undergo recycling.

Thanks