Lecture 2

Metabolism and excretion of drugs

Learning Outcomes

By the end of this lecture, students should be able to:

- Define drug metabolism.
- Describe hepatic microsomal and non-microsomal drug metabolism.
- Enumerate routes of excretion of drugs.
- Explain processes that control the urinary elimination of drugs.

Metabolism

Drugs are metabolised in the **liver,** lungs,

kidneys, blood and intestines.

- In order for drugs to pass across the lipid cell membrane they must be lipophilic.

- The higher the solubility in lipids compared to water, the more rapid the tissue entry.

- Metabolic rate determines the duration of the action of the drugs

- To excrete the drug needs to become more hydrophilic (water loving) than lipophilic.
- The speed with which a drug is metabolised will determine the duration of the action of the drug.
- This in turn will determine how often the drug is administered.

Reactions of drug metabolism

- The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules.
- Therefore, lipid-soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II.
- Phase I reactions utilizing the P450 system: Catalyzed by the cytochrome P450 system (also called microsomal mixed function oxidase).
- Cytochrome P450, designated as CYP, is composed of many families .
- Examples: CYP3A4, CYP2D6, CYP2C9/10, CYP2C19, CYP2E1, and CYP1A2.

- Phase II Reactions: This phase consists of conjugation reactions.
- If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys.
- However, many Phase I metabolites are too lipophilic to be retained in the kidney tubules.
- A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive.

Microsomal and Non microsomal Enzymes.

- Microsomal: They are located on smooth endoplasmic reticulum, mainly in liver then kidney, lungs, intestinal mucosa. They are inducible by drugs, diet. Ex- CYPs.

- Non microsomal: Non specific enzymes that catalyze few oxidative, a no. of reductive, hydrolytic and conjugation reaction.

- They are present in cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma.
- Not inducible but having polymorphism. Ex- protein oxidases, esterase, amidases etc.

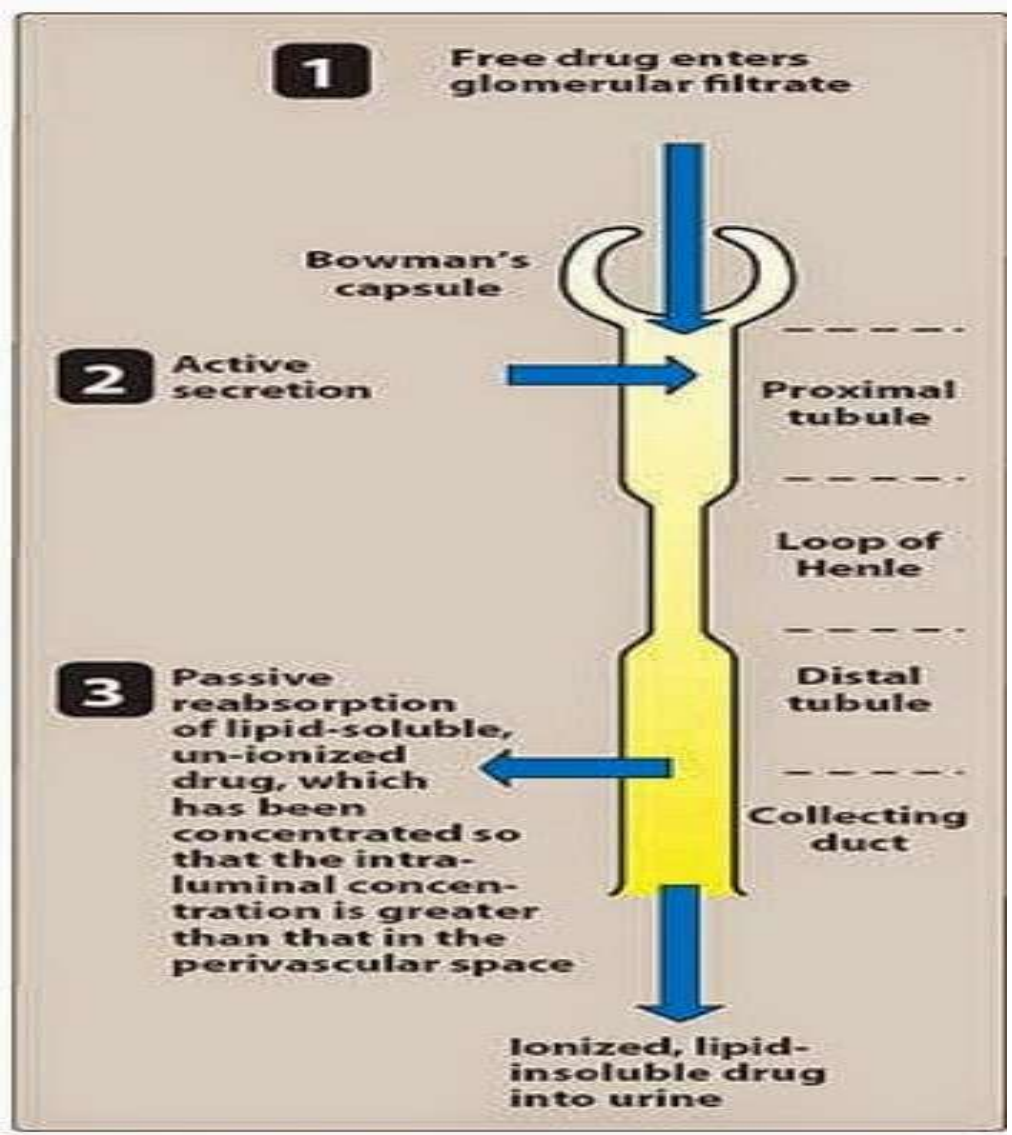
Excretion

- Drugs are **primarily** excreted by the kidneys.
- Other routes include the bile, intestine, lung, or milk in nursing mothers.
- A patient in renal failure may undergo dialysis, which removes small molecules such as drugs.
- In order for drugs to be excreted they need to become hydrophilic.
- Excretion of drugs can be affected by the urinary pH. Acidification of urine increases reabsorption and decreases excretion of weak acids, and, in contrast, decreases reabsorption of weak bases. Alkalinization of urine has the opposite effect.
- How the drug is excreted can influence prescribing decisions.

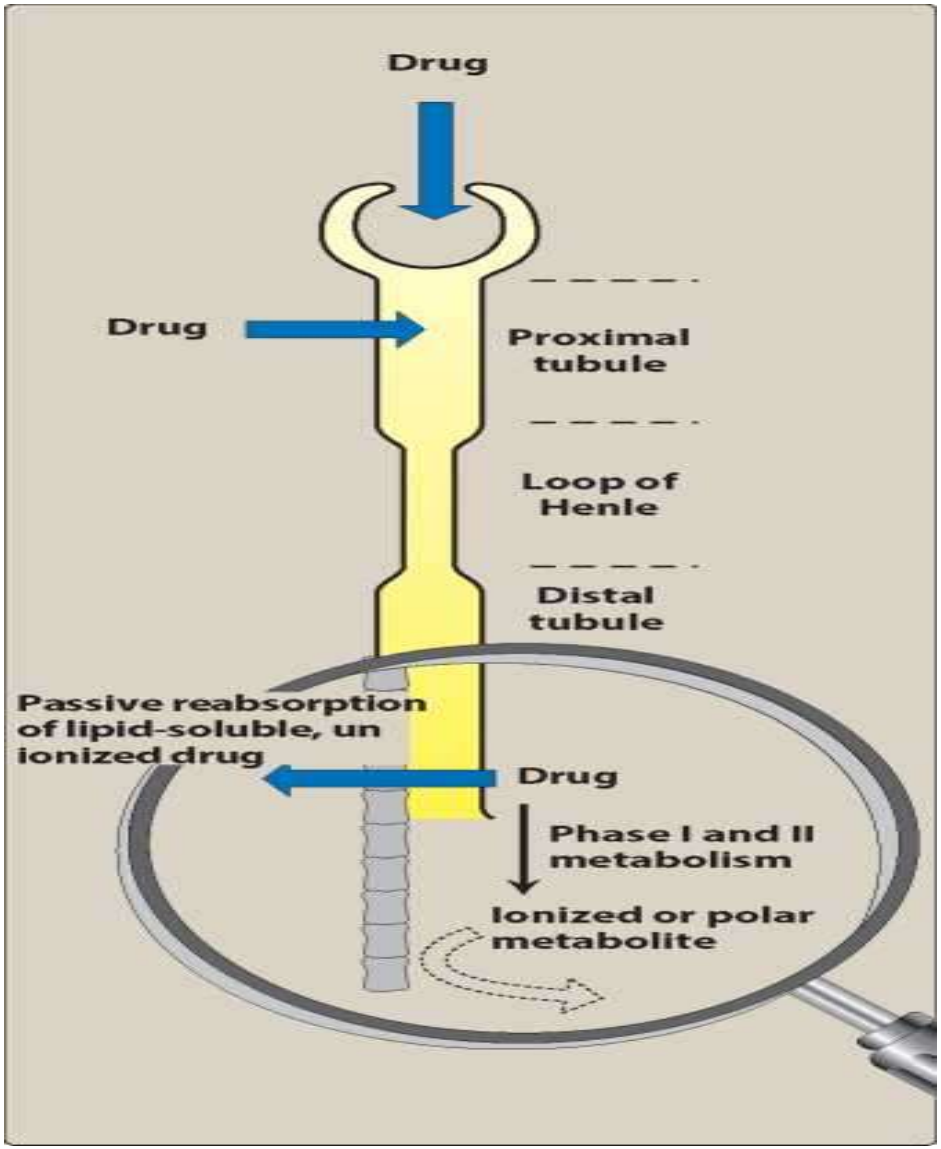
- Ageing patient with reduced renal capacity more prone to build up (toxicity) of drugs excreted renally, more of problem with drugs narrow therapeutic range e. g digoxin. some beta blockers (sotaolol) etc.

- Excretion and prescribing influence. Example: ampicillin is excreted in high concentrations in bile, so is a good choice for biliary tract infection.

Drug elimination by the kidney



Effect of drug metabolism on reabsorption in the distal tubule



Half Life of Drugs

- Drug excretion is commonly expressed in terms of half life (t1/2).

- This is the time required for the concentration of the drug in the plasma to decrease by one-half of it's initial value. Drug half life is variable and can be long or short.

- Subsequent doses are given to raise the concentration levels to a peak.
- In theory, the optimal dosage interval between drug administration is equal to the half-life of the drug.

- Half Life of Drugs – aspirin 6 hours, metronidazole 9 hours, digoxin 36 hours.
- Extensive tissue uptake, Rapid metabolism, Rapid excretion- Short half life.
- Extensive protein binding, slow metabolism, poor excretion- Long half life.
- Knowledge of half-life is essential when determining drug dose intervals.
- Concentration falls after metabolism and excretion. If dose interval is too long, effect is not achieved, too short an interval leads to toxicity.
- Ideally dose interval is equal to half life. Not practical for drugs with short half life eg penicillin.

Loading Doses

- Are used when the medical condition demands high concentrations very quickly.

- This is achieved by an initial dose that is twice the maintenance dose.

References

- Bart –Jhonson, Frank J. Dowd. ***Pharmacology and Therapeutic for Dentistry***, 6th edition, 2011. Elsevier Publishers,US
- Karen Whalen, Richard Finkel, Thomas A Panavelil. Lippincott Illustrated Reviews Pharmacology. 6th ed. 2015. Philadelphia Wolter Kluwer Puplisher