University of Basrah /College of Nursing
Branch of Basic Sciences
Pharmacology for Nurses1 (1st course)
Lecturer: Dr. Utoor Talib

Basic concepts and processes in Pharmacology

Objectives: Upon completion of this lecture, student will be able to answer the following questions:

1. Define and differentiate between Pharmacokinetics and Pharmacodynamics
2. What are pathways and mechanisms by which drugs across cell membranes
3. What are the pharmacokinetic processes and factors that affect each process.
4. Define the following terms: First Pass Effect, Bioavailability, Drug half-life, onset of action, peak concentration, duration of action. Steady state concentration, Therapeutic and toxic concentration, and Therapeutic range.

Pharmacokinetics

The most important factors that determine the intensity of drug responses: **Pharmacokinetics and Pharmacodynamics**

It's important to understand the difference between **pharmacokinetics** (drug movement\ how the body affect the drug) and **pharmacodynamics** (drug action\ how the drug affect the body)

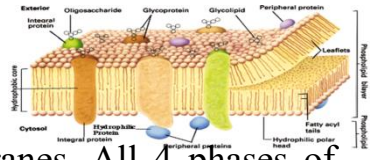
Pharmacokinetics: derived from two Greek words: *Pharmakon* = " Drug" and *Kinetics* = " Movement or Motion " **Pharmacokinetics:** the study of drug movement throughout the body.

Study what happens to the drug as it moves throughout our bodies from the time it is administered until it leaves the body.

In practical terms, it describes how the body affect the drug.

Within the body, drugs undergo several changes. From start to finish, the biological changes consist of **four drug processes** or **Pharmacokinetic processes** (abbreviated **ADME**): **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion.

QQ: What are the importance of pharmacokinetics?



QQ: How drugs move throughout the body?

To move throughout the body, drugs must cross the cell membranes. All 4 phases of pharmacokinetics (**ADME**) depend on the ability of a drug to cross membranes.

QQ: What are pathways by which drugs across cell membranes?

There are three main pathways by which drugs across cell membranes:

1) **Channels or pores**
2) **a Transport system**
3) **Direct penetration or Diffusion**

Pharmacokinetic processes:

Drug Absorption: is the process by which a drug is transferred from its site of administration to the bloodstream.

It is the process by which a drug is made available for use in the body. In case of intravenous or intra-arterial administration the drug bypasses absorption processes and it enters into the circulation directly.

Factors Affecting Drug Absorption

1) **Rate of dissolution**
2) **Surface area**
3) **Blood flow**
4) **Lipid solubility**
5) **pH partitioning:**

   acidic drugs tend to ionize and accumulate on the alkaline side

   basic drugs tend to ionize and accumulate on the acidic side

Does an increase in hydrogen increase pH?

Discuss: How the route of drug administration affects the rate and amount of absorption?

What we mean by First pass effect?

First pass effect: rapid hepatic inactivation of certain oral drugs before they reaches the systemic circulation.

A medication given orally → absorbed from the GIT → they are carried directly to the liver via the hepatic portal vein. In the liver drug may be subjected to metabolism before it reaches the systemic circulation and distributes round the body.

To circumvent the first-pass effect, a drug administered parenterally, thereby more drug reaches the circulation/ more of the drug is bioavailable and reach therapeutic levels in the systemic circulation.

The significance of first pass metabolism is limits or reduces ***a drug's bioavailability.***

Bioavailability (F): is the percentage of administered dose (the amount of drug) that reaches the systemic circulation in unchanged state to produce a biological effect (by any route).

Drugs that given IV are virtually 100% bioavailable; an oral drugs are virtually always less than 100% bioavailable because some is not absorbed from the GI tract and some undergoes first pass metabolism. Drugs with a low bioavailability may be ineffective orally and needs to be administered parenterally.

Factors affecting bioavailability:

1) Route of administration
2) Dosage form: dosage form is a major determinant of a drug's bioavailability.
3) First-pass effect.
4) Drug absorption
5) Drug solubility in gut.

Drug Distribution is defined as the movement of drugs throughout the body (drugs move between different body compartments to reach target site of action).

Once a drug is injected or absorbed into the bloodstream, it is carried by the blood and tissue fluids to its sites of pharmacologic action, metabolized, and then excreted.

Distribution depends on several factors

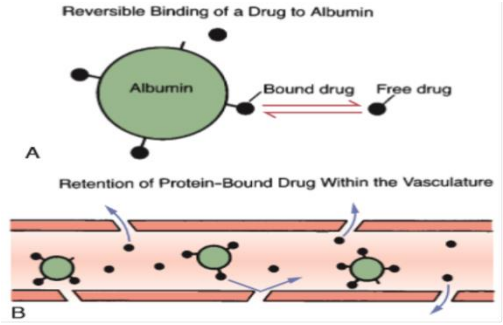
1) Drug's solubility – water or lipid soluble
2) Blood flow: Cardiac output and perfusion of the tissues – adequacy of blood circulation (good blood profusion = good flow/distribution)
   - Areas of rapid distribution: heart, liver, kidneys, brain
   - Areas of slow distribution: muscle, skin, fat
   - Peripheral vascular or cardiac disease may delay med. distribution

Organs that are well perfused (e.g. heart, liver and kidneys) will receive large amounts of drug, whereas tissues that are poorly perfused (e.g. fat, bone and muscle) will receive less drug, and it may take more time for a drug to reach levels to have a therapeutic effect.

3) Plasma proteins and tissue binding.
4) Barriers to drug distribution: Blood–brain barrier & Placental barrier

What are the consequences of plasma protein drugs binding?

1) Protein binding can restrict drug distribution.
2) Protein binding can be a source of drug interactions



Drug Metabolism (biotransformation): is defined as the enzymatic alteration of drug structure – process of chemically converting a drug to a form that is usually more easily removed from the body. This occurs primarily in the liver, but also takes place in the kidneys, lungs, bowel, and blood.

Hepatic Drug-Metabolizing Enzymes: Most drug metabolism that takes place in the liver is performed by the **hepatic microsomal enzyme system**, also known as the **P450 system**.

Three of the cytochrome P450 (CYP) families—designated **CYP1, CYP2**, and **CYP3—metabolize** drugs.

The other families metabolize endogenous compounds (e.g, steroids, fatty acids).

Each of the three P450 families that metabolize drugs is itself composed of multiple forms, each of which metabolizes only certain drugs.

Therapeutic consequences of drug metabolism

1) The most important consequence of drug metabolism **is acceleration of renal drug excretion**.
2) Drug inactivation (decreased therapeutic effect)
3) Increased therapeutic effect.
4) Activation of Pro-drugs into active forms.
5) Decreased or increased toxicity

Factors affecting the rate of drug metabolism

Several factors can influence the rate at which drugs are metabolized.

1) Age: The drug-metabolizing capacity ↓ in infant & old people.
2) Sex: males metabolized drugs more than females.
3) Genetics – genetic (inherited) allows some people to metabolize drugs rapidly and others to metabolize them more slowly.
4) Nutritional status
5) First-Pass effect
6) Induction and Inhibition of Drug-Metabolizing Enzymes.
7) Competition between drugs
8) Pathological condition

Drug Excretion is the removal of a drug and their metabolites from the body. Kidneys are the main organ of drug excretion, (especially for those that are water soluble and not volatile).

Excretion also takes place through the liver, lungs, bowel, biliary system, breast milk, and exocrine glands.

Elimination: The combination of metabolism plus excretion is called elimination.

Excretion primarily through the kidneys by:

- Glomerular filtration:
- Passive tubular reabsorption:
- Active tubular secretion or transport

Factors that modify renal drug excretion

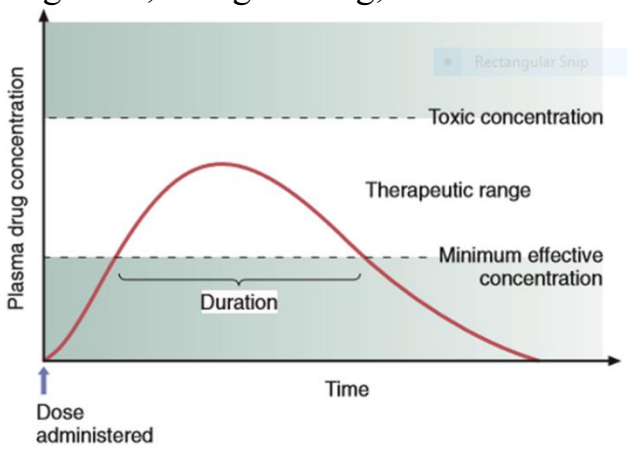
1) **PH-dependent ionization**
2) **Competition for active tubular transport**
3) **Age**
4) **Renal dysfunction**
5) **Blood flow**.

Therapeutic Drug Monitoring

Plasma Drug Levels :There is a direct relation between plasma drug levels and drug response, therefore clinicians frequently monitor plasma drug levels in efforts to regulate drug responses. When measurements indicate that drug levels are inappropriate, these levels can be adjusted up or down by changing dosage size, dosage timing, or both.

Plasma Drug Levels are of special importance:

- Minimum effective concentration
- Therapeutic concentration
- Toxic concentration.



<u>Therapeutic Index and Drug Safety</u>

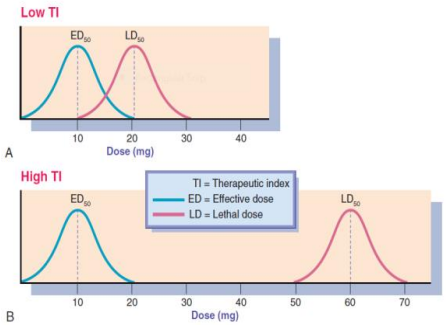
Margin of safety → serum drug concentration within therapeutic range.

Drugs with a <u>narrow or low therapeutic index</u> have a narrow margin of safety – potentially danger – small safety range between an effective dose and a toxic one, therefore, drug dosage might need adjustment, and plasma (serum) drug levels need to be monitored.

On the other hand, a drug with <u>a high therapeutic index</u> has a wide margin of safety – safe drug – and poses less risk of toxic effects. Therefore plasma (serum) drug levels do not need to be monitored routinely.

The larger the TI, the safer a drug

E.g., Penicillin has a large TI, therefore therapeutic monitoring is not needed, whereas warfarin or digoxin that has a low or small TI and must have accurate therapeutic monitoring.



Drug half-life ($t_{1/2}$) is defined as the time required for the amount of drug in the body to decrease by 50% (a percentage – not a specific amount – of drug is lost during one half-life).

A few drugs have half-lives that are extremely short—on the order of minutes. In contrast, the half-lives of some drugs exceed 1 week.

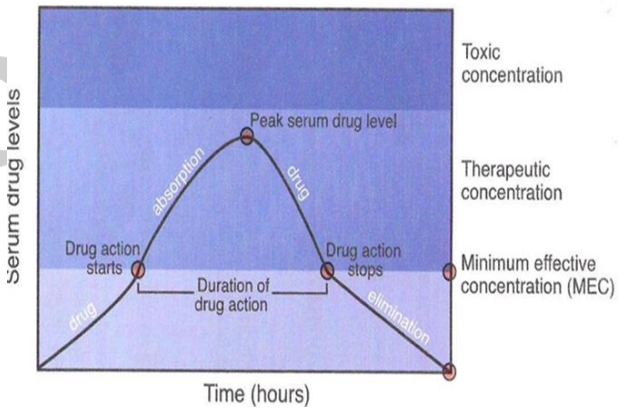
Drugs with short half-lives leave the body quickly. Drugs with long half-lives leave slowly.

Knowledge of the drug half-life is important in planning the frequency of dosing (dosing interval – how much time separates each dose).

A drug with a short half-life requires more frequent administration. Conversely, if a drug has a long half-life a long time can separates doses without loss of effects.

Plasma drug levels change over time

- **Onset of drug action**
- **peak drug level**
- **trough drug**

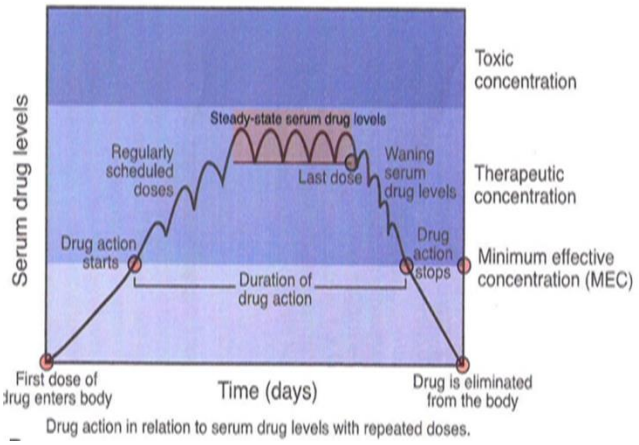


The duration of action

a **steady state or plateau**

A **loading dose**

Maintenance doses



Drug action in relation to serum drug levels with repeated doses.

Self-assessment

- What are the pharmacokinetic processes and factors that affect each process.
- Define the following terms: First Pass Effect, Bioavailability, Drug half-life, onset of action, peak concentration, duration of action. Steady state concentration, Therapeutic and toxic concentration, Therapeutic range.

References

1. Anne Collins Abrams, Clinical Drug Therapy: Rationales for Nursing Practice, 9th ed., New York, Lippincott, 2009.
2. Richard A. Lehne, Pharmacology for Nursing Care, 8th ed., London, Saunders, 2009.