BIOPHARMACEUTICS & PHARMACOKINETICS

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Biopharmaceutics is defined as the study of factors influencing the rate and amount of drug that reaches the systemic circulation and the use of this information to optimize the therapeutic efficacy of the drugs.

Pharmacokinetics is used to describe the absorption, distribution, metabolism, and excretion (ADME) of a drug.

Pharmacokinetics is the kinetics of ADME.

Pharmacokinetics refers to the movement of drugs into, through and out of the body. Intensity of effect is related to concentration of the drug at the site of action, which depends on its pharmacokinetic properties.

Pharmacokinetic properties of particular drug is important to determine the route of administration, dose, onset of action, peak action time, duration of action and frequency of dosing.

FACTORS AFFECTING ACTIVITY OF DRUGS IN THE BODY

1. Routes of drug administration
2. Dosage and dosing regimen
3. Dosage form
4. Physicochemical properties of drugs
5. Formulation parameters
6. Physiological factors

ADME

Absorption of Drugs

A drug injected intravascularly (intravenously and/or intra-arterially) directly enters the systemic circulation and exerts its pharmacological effects.

However, majority of drugs are administered extravascularly, generally orally. If intended to act systemically, such drugs can exert their pharmacological actions only when they come into blood circulation from their site of application, and for this, absorption is an important prerequisite step.

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.

Following absorption, the effectiveness of a drug can only be assessed by its concentration at the site of action.

MECHANISMS OF DRUG ABSORPTION

- Pasive Diffusion
- Active Transport
- Facilitated Diffusion
- Vesicular Transport (Endocytosis)
- Pore Transport
- Combined Absorption Mechanisms

Passive Diffusion

Also called non-ionic diffusion, it is the major process for absorption of more than 90% of the drugs.

The driving force for this process is the concentration or electrochemical gradient. *It is defined as the difference in the drug concentration on either side of the membrane*.

Drug movement is a result of the kinetic energy of molecules. Since no energy source is required, the process is called as passive diffusion.

Passive diffusion is best expressed by Fick's first law of diffusion, which states that *the drug molecules diffuse from a region of higher concentration to one of lower concentration until equilibrium is attained and that the rate of diffusion is directly proportional to the concentration gradient across the membrane*.

Active Transport

This transport process requires energy from ATP to move drug molecules from extracellular to intracellular milieu.

The mechanism involves a component of the membrane called as the carrier that binds reversibly or non-covalently with the solute molecules to be transported.

This carrier-solute complex traverses across the membrane to the other side where it dissociates and discharges the solute molecule.

Facilitated Diffusion

It is a carrier-mediated transport system that operates down the concentration gradient but at a much a faster rate than can be accounted by simple passive diffusion.

The driving force is concentration gradient (hence a passive process). Since no energy expenditure is involved, the process is not inhibited by metabolic poisons that interfere with energy production.

Examples of such a transport system include intestinal absorption of vitamins B1 and B2. A classic example of passive facilitated diffusion is the GI absorption of vitamin B12.

Vesicular Transports (Endocytosis) – Like active transport, these are also energy dependent processes but involve transport of substances within vesicles into a cell. Vesicular transport of drugs can be classed into two categories –

1. Phagocytosis (*cell eating*): adsorptive uptake of solid particulates,
2. Pinocytosis (*cell drinking*): uptake of fluid solute.

Pore Transport

It is also called as convective transport, bulk flow or filtration.

This mechanism is responsible for transport of molecules into the cell through the protein channels present in the cell membrane.

Combined Absorption Mechanisms

A drug might be absorbed by more than just one mechanism—for example, cardiac glycosides are absorbed both passively as well as by active transport.

Vitamin B12 is absorbed by passive diffusion, facilitated diffusion as well as endocytosis.

The transport mechanism also depends upon the site of drug administration.

Factors Influencing GI Absorption of a Drug from Its Dosage Form

I. Physicochemical Properties of Drug Substances

1. Drug solubility and dissolution rate
2. Particle size and effective surface area
3. Polymorphism and amorphism
4. Pseudopolymorphism (hydrates/solvates)
5. Salt form of the drug
6. Lipophilicity of the drug
7. pKa of the drug and gastrointestinal pH
8. Drug stability
9. Stereochemical nature of the drug

II. Dosage Form Characteristics and Pharmaceutical Ingredients

1. Disintegration time (tablets/capsules)
2. Dissolution time
3. Manufacturing variables
4. Pharmaceutical ingredients (excipients/adjuvants)
5. Nature and type of dosage form
6. Product age and storage conditions

III. Patient Related Factors

They include factors relating to the anatomical, physiological and pathological characteristics of the patient.

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Gastrointestinal pH
5. Disease states
6. Blood flow through the GIT
7. Gastrointestinal contents:
    a. Other drugs
    b. Food
    c. Fluids
    d. Other normal GI contents
8. Presystemic metabolism

Distribution of Drugs

Distribution *is defined as the reversible transfer of a drug between one compartment and another*. Since the process is carried out by the circulation of blood, one of the compartments is always the blood or the plasma and the other represents extravascular fluids and other body tissues.

In other words, distribution *is reversible transfer of a drug between the blood and the extravascular fluids and tissues*.

Factors Affecting Distribution of Drugs

Distribution of a drug is not uniform throughout the body because different tissues receive the drug from plasma at different rates and to different extents. Differences in drug distribution among the tissues essentially arise as result of a number of factors.

1. Tissue permeability of the drug:

- **a. Physicochemical properties of the drug like molecular size, pKa and o/w partition coefficient**
- **b. Physiological barriers to diffusion of drugs**

2. Organ/tissue size and perfusion rate

3. Binding of drugs to tissue components:

- **a. Binding of drugs to blood components**
- **b. Binding of drugs to extravascular tissue proteins**

4. Miscellaneous factors:

- **a. Age**
- **b. Pregnancy**
- **c. Obesity**
- **d. Diet**
- **e. Disease states**
- **f. Drug interactions.**

Volume of Distribution

A drug in circulation distributes to various organs and tissues. Since different tissues have different concentrations of drug, the volume of distribution cannot have a true physiologic meaning. However, there exists a constant relationship between the concentration of drug in plasma, C, and the amount of drug in the body, X.

$$X \propto C$$

$$X = V_d C$$

where Vd = proportionality constant having the unit of volume and popularly called as apparent volume of distribution. It is defined as the hypothetical volume of body fluid into which a drug is dissolved or distributed.

Vd is given by the ratio:

$$\text{Apparent Volume of Distribution} = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}}$$

or,

$$V_d = \frac{X}{C}$$

The apparent volume of distribution bears no direct relationship with the real volume of distribution.

The real volume of distribution has direct physiologic meaning and is related to the body water.

Biotransformation of Drugs

Biotransformation of drugs is defined as the chemical conversion of one form to another. The term is used synonymously with metabolism.

The pathways of drug metabolism reactions are divided into two general categories;

-Phase I reactions
-Phase II reactions

Phase I Reactions

These reactions generally precede phase II reactions and include oxidative, reductive and hydrolytic reactions. By way of these reactions, a polar functional group (-OH, -COOH, -NH2 and –SH) is either introduced or unmasked if already present on the otherwise lipid soluble substrate. The resulting product of phase I reaction is susceptible to phase II reactions.

Phase II Reactions

These reactions generally involve covalent attachment of small polar endogenous molecules such as glucuronic acid, sulphate, glycine, etc. to either unchanged drugs or phase I products having suitable functional groups (-OH, -COOH, -NH2 and –SH) and form highly water-soluble conjugates which are readily excretable by the kidneys (or bile). Thus, these reactions are called as conjugation reactions. Quite often, a phase I reaction may not yield a metabolite that is sufficiently hydrophilic or pharmacologically inert but conjugation reactions generally result in products with total loss of pharmacological activity and high polarity.

Excretion of Drugs

Drugs and/or their metabolites are removed from the body by excretion. Excretion is defined as the process whereby drugs and/or their metabolites are irreversibly transferred from internal to external environment.

Excretion of unchanged or intact drug is important in the termination of its pharmacological action.

The principal organs of excretion are kidneys. Excretion of drug by kidneys is called as renal excretion.

Excretion by organs other than kidneys such as lungs, biliary system, intestine, salivary glands and sweat glands is known as nonrenal excretion.

Renal Excretion of Drugs

The principal processes that determine the urinary excretion of a drug are;

1. Glomerular filtration.
2. Active tubular secretion.
3. Active or passive tubular reabsorption.

Glomerular filtration and active tubular secretion tend to increase the concentration of drugs in lumen and hence facilitate excretion whereas tubular reabsorption decreases it and prevents the movement of drug out of the body.

Concept of Clearance

Clearance is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared completely in a specific period of time. It is a constant for any given plasma drug concentration. In comparison to apparent volume of distribution which relates plasma drug concentration to the amount of drug in the body, clearance relates plasma concentration to the rate of drug elimination.

$$\text{Clearance (Cl)} = \frac{\text{Elimination rate}}{\text{Plasma drug concentration}}$$

Renal Clearance (ClR): **It can be defined as the volume of blood or plasma which is completely cleared of the unchanged drug by the kidney per unit time. It is expressed mathematically as:**

$$Cl_R = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug concentration}}$$

Non-renal Routes of Drug Excretion

Drugs and their metabolites may also be excreted by routes other than the renal route, called as the extrarenal or nonrenal routes of drug excretion. The various such excretion processes are:

1. **Biliary excretion**
2. **Pulmonary excretion**
3. **Salivary excretion**
4. **Mammary excretion**
5. **Skin/dermal excretion**
6. **Gastrointestinal excretion**
7. **Genital excretion**