UNIT-I

Introduction/ Basic Concepts Of Pharmacology

Pharmacology

Definition of Pharmacology

It is defined as the study of substances, that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting the normal body processes.

Branches of Pharmacology

Pharmacokinetics
Study of effects the body has on drugs, includes absorption, distribution, metabolism and excretion is called Pharmacokinetics.

Pharmacodynamics
Study of effects of drugs on the body is called Pharmacodynamics.

Pharmacokinetics

Before discussing the Pharmacokinetics, it is important to understand about the routes of drug administration.

Routes Of Drug Administration

The route of drug administration is determined primarily by

- The properties of drug (water or lipid solubility, ionization etc)
- The therapeutics objectives (the desirability of a rapid onset of action or the need for long term administration)

There are three major routes of drug administration

1. **Enteral (oral, sublingual)**
2. **Parenteral (IV, IM, SC etc.)**
3. **Others (inhalation, intranasal, topical etc.)**

Enteral

Enteral administration is the simplest and most common means of administration drug, enteral route includes…

1. **Oral**
2. **Sublingual**

Oral route
Giving drug by mouth is called oral route.

Advantages

- Most convenient and most acceptable
- Used for local as well as systemic action of drugs.
- Dosage forms do not require sterile techniques for administration.

- Delivery of drug into circulation is slow, so that rapid, high blood concentration are avoided and adverse effects are less

Disadvantages

- Rate of absorption is variable
- Irritation of mucosal surfaces can occur
- Extensive hepatic metabolism (first pass effect) may occur before the drug reaches its site of action
- Onset of action is delayed, thus unsuitable in emergency situation
- Drugs destroyed by digestive enzymes (insulin, pituitary hormones) or by gastric acidity (benzyl penicillin) cannot be administration

Sublingual

Placement of drug under the tongue is called sublingual, it allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly.

Advantages

- Rapid absorption and effect (eg, glyceryl trinitrate in angina)
- Spitting out tablet can terminate effect
- Low incidence of infection
- Avoidance of first pass metabolism

Disadvantages

- Inconvenient (discomfortable) for frequent use
- Irritation of oral mucosa, and excessive salivation

Parenteral

Parenteral administration is used for drugs that are poorly absorbed from the GIT (heparin) and for agents that are unstable in the GIT (insulin). Parenteral administration is also used for treatment of unconscious patients and under situations that require a rapid onset of action.

Examples

- Intravenous (IV)
- Intramuscular (IM)
- Intra dermal (ID)
- Subcutaneous (SC)
- Intra peritoneal (IP)
- Intra arterial (IA)
- Intra cardiac (IC)
- Intra thecal (IT)
- Intra articular or joint (IJ)
- Intra bone marrow (IBM)

The tree major parental routes are intravenous, intramuscular and subcutaneous

Advantages

- Drugs get to the site of action more rapidly, providing a rapid response, which may be required in an emergency
- Dose can be more accurately delivered
- Suitable for drugs that are not absorbed from GIT

Disadvantages

- More rapid absorption can lead to increased adverse effects
- Local irritation may occur at the site of injection
- These routes are irreversible and may cause pain, fear, and infection

Other Routes Of Drug Administration

- **Inhalation**
- **Intranasal**
- **Topical**
- **Rectal**

Drug Absorption

Absorption is transfer of a drug from its site of administration to the bloodstream. The rate and efficiency of absorption depend on the route of administration. For IV delivery, absorption is complete, that is the total dose of drug reaches the system circulation.

Transport Of A Drug From The GI Tract

Depending on their chemical properties, drug may be absorbed from the GI tract by either passive diffusion or active transport.

Passive Diffusion

It refers to passage of drug molecules by diffusing a un-ionized moiety through lipid membrane. The drug moves from a region of high concentration to one of lower concentration. The vast majority of drug gains access to the body by this mechanism.

Active Transport

Active transport is energy dependent and is driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient that is from a region of low drug concentration to one of higher drug concentration.

Endocytosis And Exocytosis

This type of drug delivery transports drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug filled vesicle. Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process.

Drug Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream, and enters the interstitium (extracellular fluid) and/ or the cell of the tissues.

Blood Flow

The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs. Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles; adipose tissue has a still lower rate of blood flow. More drugs are delivered to greater blood flow areas.

Capillary Permeability

- It varies widely in various tissues
- In brain capillary endothelial cells are continuous and have no slit junction, so that only lipid soluble (unionized) drug can cross.

- In liver and spleen a large part of basement membrane is exposed by large discontinuous capillary through which large plasma protein can pass.

Binding Of Drug To Plasma Protein
Drug molecules may bind to plasma protein (usually albumin). Bound drugs are pharmacologically inactive, only the free, unbound drug can act on target site in the tissues. Bound drug stays in vascular space and is not metabolized or eliminated.

Apparent Volume Of Distribution
A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular compartments. For example, lipids (abundant in adipocytes and cell membranes), protein (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells). Therefore, the volume into which drugs distribute is called the apparent volume of distribution.

VD = Dose administered / Plasma Concentration of drug

Drug Metabolism

Drugs are most eliminated by biotransformation and/or excretion into the urine or bile. The process of metabolism transforms lipophilic drugs into more polar readily excretable products. The liver is the major site for drug metabolism, but specific drug may undergo biotransformation in other tissues, such as the kidney and the intestine.

Reaction Of Drug Metabolism
The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membrane and are reabsorbed in the distal tubules. Therefore lipid soluble agents must first be metabolized in the liver using two general sets of reaction, called Phase I and Phase II.

Phase I
Phase-I reaction function to convert lipophilic molecules into more polar molecules by the exposing a polar functional group. Mainly it is oxidation, but sometimes there is reduction or hydrolysis.

Phase II
This phase consists of conjugation reactions. If the metabolites 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 kidneys tubules. A subsequent conjugation reaction with an endogenous substrate such as sulfuric acid, acetic acid, or amino acid result in polar and more water soluble compounds, that excreted by the kidney.

Drug Elimination

Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung or milk in nursing mothers. A patient in renal failure may undergo extracorporeal dialysis, which removes small molecules such as drug.

Routes of Elimination

Kidney
Excretion of drug and their metabolites into urine involves:

- Glomerular filtration e.g. of water soluble and polar components (less than 500 dalton)
- Active tubular secretion
- Passive tubular reabsorption

Liver
It can secrete drugs or their metabolites into bile that are lost in feces. However, some drug may be reabsorbed in intestine to again enter the circulation.

GIT
Some drugs are excrete through GIT
Thiocynates, iodides and mercury in saliva
Morphine through passive diffusion in stomach

Lungs
Gaseous and volatile general anesthetic is excreted in expired air.

Others Routes
- Sweat
- Tears
- Breast milk
- Salivary secretion

Pharmacodynamics

Most drugs exert their effects, both beneficial and harmful, by interacting with receptors that are, specialized target macromolecules present on the cell surface or intracellulraly. Receptors bind drugs and initiate events leading to alterations in biochemical and / or biophysical activity of a cell and consequently, the function of an organ. Drugs may interact with receptors in many different ways. Drugs may bind to enzymes, nucleic acids or membrane receptors.

Major Receptors Families

Pharmacology defines receptors as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes and structural protein can be considered to be pharmacological receptors.

Ligand-Gated Ion Channels Receptors
These are responsible for regulation of the flow of ion across cell membrane. The activity of these channels is regulated by the binding of a ligand to the channel.
Nicotinic receptor (Nn, Nm) and Gamma aminobutyric acid (GABA) receptors are important examples of ligand-gated receptors.

G-Protein Coupled Receptors
A second family of receptors consists of G protein-coupled receptors. These receptors contain a single peptide; these receptors are linked to a G protein having three subunits, alpha, beta, and gamma subunit. Binding of the appropriate ligand to the extra-cellular region of the receptor activates the G protein.

Enzyme Linked Receptors
A third major family of receptors consists of those having cytosolic enzyme activity as an integral component of their structure or function. Binding of a ligand activates or inhibits this cytosolic enzyme activity.

Intracellular Receptors
The fourth family of receptors is called intra cellular receptors. These receptors are either in the cytoplasm or in the nucleolus gives response by increasing the gene transcription.