***Pharmacology***

***College of Al- Mustaqbal universal***

***Definitions and general principles of pharmacology***

***Done by specialist pharmacist :***

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**Introduction to Phrmacology**

The word “pharmacology” is derived from the words *pharmakon*, which

means “drug” and *logus*, which means “science.”

**Pharmacology** is the science of the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient.

**Drugs** are chemical substances which affect living organisms and are used

by the clinician to diagnose, prevent, or cure diseases. So the safe use

of drugs needs sound knowledge of their various aspects such as mechanism

of action, doses, routes of administration, adverse drug affects, toxicity,

and drug interactions

**Pharmacodynamics:** The study of the biological and therapeutic effects of drugs (i.e,“what the drug does to the body”).

**Pharmacokinetics:** Study of the absorption, distribution metabolism and excretion

(ADME) of drugs (“i.e what the body does to the drug”).

**Toxicology:** It’s the science of poisons. Many drugs in larger doses may act as poisons.

**Poisons** are substances that cause harmful, dangerous or fatal symptoms in living

substances.

**Sources of Drugs:**

1. **Animals:** Insulin, thyroid extract, heparin and antitoxin sera, etc.

2. **Plants:** Morphine, digoxin, atropine, castor oil, etc.

3. **Minerals:** Liquid paraffin, magnesium sulfate, magnesium trisilicate, kaolin, etc.

4. **Synthetic source:** Aspirin, sulphonamides, paracetamol, zidovudine, etc.

5. **Micro organisms:** Penicillin, streptomycin and many other antibiotics.

6. **Genetic engineering:** Human insulin, human growth hormone etc.

**Pharmacodynamics**

Involves how the drugs act on target cells to alter cellular function.

**A. Receptor and non-receptor mechanisms:** Most of the drugs act by interacting with acellular component called receptor. Some drugs act through simple physical or chemical reactions without interacting with any receptor.

**Receptors** are protein molecules present either on the cell surface or with in the cell

e.g. adrenergic receptors, cholinoceptors, insulin receptors, etc.

• The endogenous neurotransmitters, hormones, autacoids and most of the drugs

produce their effects by binding with their specific receptors.

• Aluminium hydroxide and magnesium trisilicate, which are used in the treatment of peptic ulcer disease act by non-receptor mechanism by neutralizing the gastric acid.

Many drugs are similar to or have similar chemical groups to the naturally occurring chemical and have the ability to bind onto a receptor where one of two things can happen- either the receptor will respond or it will be blocked.

A drug, which is able to fit onto a receptor, is said to have affinity for that receptor. **Efficacy** is the ability of a drug to produce an effect at a receptor. An agonist has both an affinity and efficacy whereas antagonist has affinity but not efficacy or intrinsic activity.

When a drug is able to stimulate a receptor, it is known as an agonist and therefore mimics the endogenous transmitter.

When the drug blocks a receptor, it is known as antagonist and therefore blocks the action of the endogenous transmitter (i.e. it will prevent the natural chemical from acting on the receptor).

However, as most drug binding is reversible, there will be competition between the drug and the natural stimulus to the receptor.

The forces that attract the drug to its receptor are termed chemical bonds and they are:

(a)hydrogen bond (b) ionic bond (c) covalent bond (d) Vander waals force. Covalent bond is the

strongest bond and the drug-receptor complex is usually irreversible.

**Pharmacokinetics**

Pharmacokinetics deals with the absorption, distribution, metabolism and excretion drugs in the body.

***A. Biotransport of drug***: It is translocation of a solute from one side of the biological barrier to the other.

**1. Structure of biological membrane:** The outer surface of the cell covered by a very thin structure known as plasma membrane. It is composed of lipid and protein molecules.

membrane proteins have many functions like (a) contributing structure to the membrane

(b) acting as enzyme (c) acting as carrier for transport of substances (d) acting as receptors.

The plasma membrane is a semipermeable membrane allowing certain chemical

substances to pass freely e.g. it allows water, glucose, etc. but it won’t allow sucrose until it

is converted into glucose and fructose.

**2. Passage of drug across membrane.**

(a) Passive transfer

i) Simple diffusion

ii) Filtration

(b) Specialized transport

i) Facilitated diffusion

ii) Active transport

iii) Endocytosis

***i) Simple diffusion:*** Movement of a solute through a biological barrier from the phase of

higher concentration to phase of lower concentration. No need of energy e.g. highly

lipid soluble drugs.

***ii) Filtration:*** Is the process by which water soluble drug of relatively low molecular

weight crosses the plasma membrane through pores as a result of hydrodynamic

pressure gradient across the membrane e.g. urea and ethylene glycol

***i) Facilitated diffusion***: It means the passage of drug across the biological membrane

along the concentration gradient by the protein carrier mediated system also called as

carrier mediated diffusion. It depends on number of carrier e.g. tetracycline, pyrimidine.

***ii) Active transport:*** The process by which drugs pass across the biological membrane

most often against their concentration gradient with the help of carriers along with the expenditure of energy e.g. alpha methyl dopa, levodopa, 5-fluoro-uracil, 5 bromouracil.

***iii) Endocytosis:*** It is the process by which the large molecules are engulfed by the cell membrane and releases them intracellularly e.g. protein, toxins (botulinum, diphtheria)

**B. Drug absorption:** Absorption is the process by which the drug enters in to the systemic circulation from the site of administration through biological barrier. In case of intravenous or intra-arterial administration the drug bypasses absorption processes and it enters into the circulation directly.

**1. Routes of drug administration:**

**a) From the alimentary tract:**

(i) Buccal cavity: e.g. nitrates

(ii) Stomach: e.g. aspirin, alcohol

(iii) Intestine: e.g. most of non ionized and ionized drugs.

(iv) Rectum: e.g. rectal suppositories, bisacodyl laxatives.

**Advantages of oral route:** This route is safe, convenient and economical.

**Disadvantages of oral route:** Onset of drug action is slow, irritant drugs cannot be

administered and it is not useful in vomiting and severe diarrhea, gastric acid and digestive enzymes may destroy some drugs, and water soluble drugs are absorbed poorly

**b) From the parenteral route:**

(i) **Intradermal**: This is given into the layers of the skin e.g. B.C.G. vaccine

(ii) **Subcutaneous**: Non-irritant substances are given into subcutaneous tissue

e.g. insulin

(iii) **Intramuscular**: Soluble substances, mild irritants, suspensions and colloids can be injected by this route. These injections can be given to deltoid or gluteal muscle. This route is one of the more common routes e.g. multivitamins, streptomycin, etc.

**Advantages:** rate of absorption is uniform, onset of action is faster than oral and

it can be given in diarrhoea or vomiting.

**Disadvantages:** Pain at local site of injection, the volume of injection should not

exceed 10 ml.

(iv) **Intravenous**: Drugs directly given into a vein, produce rapid action, no need of absorption as they enter directly into blood, can be given as bolus e.g. furosemide,morphine, dopamine or as continous infusion e.g. fluids during shock or dehydration.

**Advantages:** It can be given in large volumes, production of desired blood

concentration can be obtained with a well designed dose.

**Disadvantages:** Drug effect cannot be halted if once the drug is injected,

expertise is needed to give injection.

(v) **Intrathecal**: Injected into subarachnoid space of spinal cord e.g. spinal anaesthetics.

(vi) **Intraperitonial**: Injections given into the abdominal cavity e.g. infant saline, glucose.

(vii) **Intra-articular**: Injected directly into a joint e.g. hydrocortisone.

**d) Topical/ local route:** The absorption through skin is a passive process. The absorption occurs more easily throughthe cell lining e.g. dusting powder, paste, lotion, drops, ointment, suppository for vagina and rectum.

**e) Inhalation:**

Drugs may be administered as dry powders, and nebulized particles when sprayed as fine droplets get deposited over the mucous membrane producing local effects and may be absorbed for systemic effects e.g. salbutamol spray used in bronchial asthma and volatile general anaesthetics.

**2. Bioavailability:**

It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given IV, the bioavailability is 100%. It is important to know the manner in which a drug is absorbed. The route of administration largely determines the latent period between administration and onset ofaction. Drugs given by mouth may be inactive for the following reasons:

a) Enzymatic degradation of polypeptides within the lumen of the gastrointestinal tract e.g. insulin, ACTH.

b) Poor absorption through gastrointestinal tract e.g. aminoglycoside antibiotic.

c) Inactivation by liver e.g. testosterone during first passage through the liver before it reaches systemic circulation

**3. Factors affecting drug absorption and bioavailability:**

a) Physico-chemical properties of drug

b) Nature of the dosage form

c) Physiological factors

d) Pharmacogenetic factors

e) Disease states.

**a) Physico-chemical properties of drug:**

i) **Physical state**: Liquids are absorbed better than solids and crystalloids absorbed better than colloids.

ii) **Lipid or water solubility**: Drugs in aqueous solution mix more readily than those in oily solution. However at the cell surface, the lipid soluble drugs penetrate into the cell more rapidly than the water soluble drugs.

iii) **Ionization:** Most of the drugs are organic compounds. Unlike inorganic compounds, the organic drugs are not completely ionized in the fluid. Unionized component is predominantly lipid soluble and is absorbed rapidly and an ionized is often water soluble component which is absorbed poorly. Most of the drugs are weak acids or weak bases.

It may be assumed for all practical purposes, that the mucosal lining of the G.I.T is

impermeable to the ionized form of a weak organic acid or a weak organic base. These drugs exist in two forms.

**Acidic drugs**: rapidly absorbed from the stomach e.g. salicylates and barbiturates.

**Basic drugs**: Not absorbed until they reach to the alkaline environment i.e. small

intestine when administered orally e.g. pethidine and ephedrine

**b) Dosage forms:**

i) **Particle size:** Small particle size is important for drug absorption.

Drugs given in a dispersed or emulsified state are absorbed better e.g. vitamin D and vitamin A.

ii) **Disintegration time and dissolution rate.**

Disintegration time: The rate of break up of the tablet or capsule into the drug granules.

Dissolution rate: The rate at which the drug goes into solution

iii) **Formulation:** Usually substances like lactose, sucrose, starch and calcium phosphate are used as inert diluents in formulating powders or tablets. Fillers may not be totally inert but may affect the absorption as well as stability of the medicament. Thus a faulty formulation can render a useful drug totally useless therapeutically.

**c) Physiological factors:**

i) **Gastrointestinal transit time:** Rapid absorption occurs when the drug is given on empty stomach. However certain irritant drugs like salicylates and iron preparations are deliberately administred after food to minimize the gastrointestinal irritation. But some times the presence of food in the G.I tract aids the absorption of certain drugs e.g. griseofulvin, propranolol and riboflavin.

ii) **Presence of other agents:** Vitamin C enhances the absorption of iron from the G.I.T. Calcium present in milk and in antacids forms insoluble complexes with the tetracycline antibiotics and reduces their absorption.

iii) **Area of the absorbing surface and local circulation:** Drugs can be absorbed better from the small intestine than from the stomach because of the larger surface area of the former. Increased vascular supply can increase the absorption.

iv) **Enterohepatic cycling:** Some drugs move in between intestines and liver before they reach the site of action. This increases the bioavailability e.g. phenolphthalein.

v) **Metabolism of drug/first pass effect:** Rapid degradation of a drug by the liver during the first pass (propranolol) or by the gut wall (isoprenaline) also affects the bioavailability.Thus a drug though absorbed well when given orally may not be effective because of its extensive first pass metabolism.

**d) Pharmacogenetic factors:**

Individual variations occur due to the genetically mediated reason in drug absorption and response.

**e) Disease states:**

Absorption and first pass metabolism may be affected in conditions like malabsorption, thyrotoxicosis, achlorhydria and liver cirrhosis.

**C) Distribution of drugs**

1. **Definition**: Penetration of a drug to the sites of action through the walls of blood vessels fro the administered site after absorption is called drug distribution. Drugs distribute through various body fluid compartments such as (a) plasma (b) interstitial fluid compartment (c) trans-cellular compartment.

**Apparent Volume of distribution (VD):** The volume into which the total amount of a drug in the body would have to be uniformly distributed to provide the concentration of the drug actually measured in the plasma. It is an apparent rather than real volume.

**Factors determining the rate of distribution of drugs:**

1**. Protein binding of drug:** A variable and other significant portion of absorbed drug may become reversibly bound to plasma proteins. The active concentration of the drug is that part which is not bound, because it is only this fraction which is free to leave the plasma and site of action. (a) Free drug leave plasma to site of action (b) binding of drugs to plasma proteins assists absorption (c) protein binding acts as a temporary store of a drug and tends to prevent large fluctuations in concentration of unbound drug in the body fluids (d) protein binding reduces diffusion of drug into the cell and there by delays its metabolic degradation

e.g. high protein bound drug like phenylbutazone is long acting.

Low protein bound drug like thiopental sodium is short acting

2**. Plasma concentration of drug (PC):** It represents the drug that is bound to the plasma proteins (albumins and globulins) and the drug in free form. It is the free form of drug that is distributed to the tissues and fluids and takes part in producing pharmacological effects.

The concentration of free drug in plasma does not always remain in the same level e.g.

i) After I.V. administration plasma concentration falls sharply

ii) After oral administration plasma concentration rises and falls gradually.

iii) After sublingual administration plasma concentration rise sharply and falls gradually.

3. **Clearance:** Volume of plasma cleared off the drug by metabolism and excretion per unit time.

Protein binding reduces the amount of drug available for filtration at the glomeruli and hence delays the excretion, thus the protein binding reduces the clearance.

4. **Physiological barriers to distribution**: There are some specialized barriers in the body due to which the drug will not be distributed uniformly in all the tissues. These barriers are:

a) **Blood brain barrier (BBB)** through which thiopental sodium is easily crossed but not dopamine.

b) **Placental barrier:** which allows non-ionized drugs with high lipid/water partition coefficient by a process of simple diffusion to the foetus e.g. alcohol, morphine

5. **Affinity of drugs to certain organs:** The concentration of a drug in certain tissues after asingle dose may persist even when its plasma concentration is reduced to low. Thus the hepatic concentration of mepacrine is more than 200 times that of plasma level. Their concentration may reach a very high level on chronic administration. Iodine is similarly concentrated in the thyroid tissue.

**D. Metabolism of drugs:**

Drugs are chemical substances, which interact with living organisms and produce some pharmacological effects and then, they should be eliminated from the body unchanged or by changing to some easily excretable molecules. The process by which the body brings about changes in drug molecule is referred as drug metabolism or biotransformation

**Enzymes responsible for metabolism of drugs:**

a) **Microsomal enzymes:** Present in the smooth endoplasmic reticulum of the liver, kidney and GIT e.g. glucuronyl transferase, dehydrogenase , hydroxylase and cytochrome P450

b) **Non-microsomal enzymes:** Present in the cytoplasm, mitochondria of different organs. e.g. esterases, amidase, hydrolase.

**Types of biotransformation:** The chemical reactions involved in biotransformation are classified as phase-I and phase – II (conjugation) reactions. In phase-I reaction the drug is converted to more polar metabolite. If this metabolite is sufficiently polar, then it will be excreted in urine. Some metabolites may not be excreted and further metabolised by phase –II reactions.

Phase-I: Oxidation, reduction and hydrolysis.

Phase-II: Glucuronidation, sulfate conjugation, acetylation, glycine conjugation and methylation reactions.

**Phase - I reactions**

a) **Oxidation:** Microsomal oxidation involves the introduction of an oxygen and/or the removal of a hydrogen atom or hydroxylation, dealkylation or demethylation of drug molecule e.g. conversion of salicylic acid into gentisic acid.

b) **Reduction:** The reduction reaction will take place by the enzyme reductase which catalyze the reduction of azo (-N=N-) and nitro (-NO2) compounds e.g. prontosil converted to sulfonamide.

c) **Hydrolysis:** Drug metabolism by hydrolysis is restricted to esters and amines (by esterases and amidases) are found in plasma and other tissues like liver. It means splitting of drug molecule after adding water e.g. pethidine undergoes hydrolysis to form pethidinic acid.

Other drugs which undergo hydrolysis are atropine and acetylcholine.

**Phase - II reactions** (conjugation reactions):

This is synthetic process by which a drug or its metabolite is combined with an endogenous substance resulting in various conjugates such as glucoronide, ethereal sulfate, methylated compound and amino acid conjugates.

**Glucuronide conjugation**: It is the most common and most important conjugation reaction of drugs. Drugs which contain

a) Hydroxyl, amino or carboxyl group undergo this process e.g. phenobarbitone.

b) Sulfate conjugation: Sulfotransferase present in liver, intestinal mucosa and kidney, which transfers sulfate group to the drug molecules e.g. phenols, catechols, etc.