Pharmacology

Pharmacology: A study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes or (is the study of the therapeutic value and/or potential toxicity of chemical agents on biological systems. It targets every aspect of the mechanisms for the chemical actions of both traditional and novel therapeutic agents).

- **Systemic Pharmacology**: studying the effect of drug or group of drugs on a determined system of living organism. Ex, Neuropharmacology, Cardiovascular pharmacology,…..etc.
- **Molecular pharmacology**: deals with the biochemical and biophysical characteristics of interactions between drug molecules and those of the cell.
- **Clinical pharmacology**: is the application of pharmacodynamics and pharmacokinetics to patients with diseases.
  - **Pharmacokinetics**: the manner in which the body handles a drug, or (what the body does to the drug).
  - **Pharmacodynamic:** the relationship between the drug concentration and effect (what the drug does to the body).
- **Veterinary pharmacology**: concerns the use of drugs for diseases and health problems unique to animals.
- **Toxicology:** is that branch of pharmacology which deals with the undesirable effects of chemicals (poisons) or toxins on living systems.

Note\ Often confused with pharmacology, pharmacy is a separate field in the health sciences. It is the profession responsible for the preparation, dispensing and appropriate use of medication, and provides services to achieve optimal therapeutic outcomes.

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Routes of drug administration:

- **Enteral** (Oral) :- like Tablets, Solutions, Suspensions .
- **Parentral**:- by injections

And it's classified according to the speed of stimulation to the drug in to four ways those are:-

- ✓ **Intravenous injection (i.v.).**
- ✓ **Intraperitonial injection (i.p.).**
- ✓ **Intramuscular injection (i.m.).**
- ✓ **Subcutaneous injection (s/c).**

- **Topical** administration or (local) :-

And includes:-

- ❖ **On skin.**
- ❖ **In the eye.**
- ❖ **Intravaginal.**

Other special routes include:-

- ➢ **Inhalation** (Respiratory system).
- ➢ **Intrathecal** (epidural anesthesia in spinal cord).
- ➢ **Sublingual**.

Methods of transport of drug across cell membrane:

There are two main methods of transport of material across cell membrane :-

1. **Passive :**(the membrane plays no role in the process , transport follows concentration gradients , from high concentration to low concentration) . this consist of :
    a) **Filtration** : means passing through pores . Example lithium.
    b) **Simple Diffusion**: the molecules get dissolved in the lipoid membrane so must be lipid soluble). example (weak acids, weak basis).

2. **specialized** : consist of
    a) **Active Transport**: requires energy and carrier , work against concentration gradient , from low concentration to high concentration) . example (execration of penicillin through the proximal convoluted tubules).
    b) **Facilitated Transport**: requires carrier only , obeys concentration gradient . example Amino acids.
    c) **Pinocytosis** : engulfing large molecules like protein , rare for drug .

Drug molecules mostly pass through cell membrane by passive method , therefore , lipid solubility is an important factor in determining the rate of passage though this barrier and ultimately plays role in the rate of all four pharmacokintical processes that is absorption , distribution , metabolism and excretion .

The Pharmacokinetics: the manner in which the body handles a drug or Examines the rate at which drug concentrations change in the body by observing , study of pharmacokinetic is necessary to estimate drug level and ultimately determine the right dose .

Input processes

• **Absorption**: movement of drug into the body from the site of administration

Output processes*:* responsible for drug delivery and removal from the body

• **Distribution**: movement of drug from intravascular to extravascular compartment .

• **Metabolism**: chemical transformation of drug .

• **Elimination**: removal of drug from the body .

Absorption

The process of transport of drug molecules from site of administration to blood circulation , most drugs are absorbed into the systemic circulation via passive diffusion other mechanisms of absorption include: active transport, facilitated diffusion .

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Absorption after oral administration :

Drug administration orally can be absorbed from any area of the GIT mucosa . however , the usual sites of absorption are the stomach and the upper part of the small intestine . The method of transport of the drug molecules from the GIT lumen to blood circulation is achieved by two steps :

1. From the lumen to the extra cellular fluid (by simple diffusion , require lipid solubility).
2. From the extra cellular fluid to the blood circulation (by simple diffusion and filtration through the large pores present in the endothelial cells of the blood capillaries) .

Absorption rate and amount depends on

- Local blood flow at administration site(e.g. sublingual vessels provide significant blood flow therefore rapid absorption)
- Lipid solubility: greater lipid solubility = increased rate of diffusion through membranes (e.g. anesthetics are very lipid soluble therefore have a rapid onset of action) .
- Molecular size: small size, water soluble drugs can pass through channels in membranes, Large molecules cannot(e.g. aminoglycosides are large molecules and are not absorbed through intestinal mucosa and are therefore not orally active) .
- Local pH and drug ionization: charged molecules do not cross membranes e.g. lactulose ionizes ammonia to ammonium and keeps it in the bowel .
- Total surface area for absorption: the small intestine has villi which increase the surface area for absorption, and hence is the primary site of absorption for most oral drugs.

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Henderson-Hesselbach Equation:

The proportion of the total drug concentration that is present in either ionized orun-ionized form is dictated by the drug's dissociation or ionization constant (K) and the local pH of the solution in which the drug is dissolved.

The dissociation of a weak acid, RH, and a weak base, B, is described by the following equations:

$$RH \rightleftharpoons H^+ + R^- \text{ (acid)}$$
$$B + H^+ \rightleftharpoons BH^+ \text{ (base)}$$

If these equations are rewritten in terms of their dissociation constants (using Ka for both weak acids and weak bases), we obtain:

$$K_a = \frac{[R^-][H^+]}{[RH]} \text{ (acid)}$$

$$K_a = \frac{[H^+][B]}{[BH^+]} \text{ (base)}$$

By taking logarithms and then substituting the terms pK and pH for the negative logarithms of Ka and $[H^-]$, respectively, we arrive at the *Henderson-Hasselbach equations:*

$$pH = pK_a + \log\frac{[R^-]}{[RH]} \text{ (acid)}$$

and

$$pH = pK_a + \log\frac{[B]}{[BH^+]} \text{ (base)}$$

And we can simplify these two formulas to:

- **For weak acids drugs**: $PH - Pka = \log \frac{\text{Ionized}}{\text{Unionized}}$

- **For weak bases drugs**: $PH - Pka = \log \frac{\text{Unionized}}{\text{Ionized}}$

Factors which affect drug absorption:-

1. The chemical nature of drug.
2. Pharmaceutical form of the drug.
3. Dissociation constant PKa of the drug.
4. PH of the medium.
5. Presence or absence of food.
6. Movement of gastro-intestinal tract (G.I.T).
7. Nature of the food.
8. Species of animal.

Bioavailability (F):A fraction of the drug which reach to the circulation after administration from any route other than the (i.v.) route, for example if 100mg of drug administrated orally and 70mg of this drug is absorbed unchanged, the bioavailability is 70%.

$$\textbf{Bioavailability (F)} = \frac{\text{Amount drug in any route of administration}}{\text{Amount of drug after intravenous administration}} \times 100\ (\%)$$

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First pass effect: Metabolism of orally administered drug in the liver before it reaches the systemic circulation. That's to say if a drug with high first pass effect it means low bioavailability and vise versa (inverse proportion). drugs with a high first-pass effect include: chlorpromazine levodopa, morphine, propranolol, lidocaine, hydralazine, nortriptyline, and organic nitrates, drugs with low hepatic extraction (little or no first pass effect) include diazepam, digoxin, phenylbutazone, phenytoin, theophylline, tolbutamide, warfarin .

Distribution:

Movement of drug from intravascular to extravascular compartment or process by which drugs are carried throughout the body to reach target sites of action.

Factors effect on the drug distribution:

1. Blood flow: drug molecules are highly distributed to the highly vascularized tissues like brain, liver, and kidney.
2. Capillary permeability: capillaries of some organs (Brain, Testes, Placenta) have tight pores there for only lipid soluble materials can pass by simple diffusion.
3. Chemical nature of the drug: its play an important role in drug distribution, so the non-polar drugs are well distributed across tissues while polar drugs are not well distributed across tissues.
4. Binding of drug to plasma proteins: drugs with high affinity to bind to plasma proteins have low distribution, and this binding will slow there transfer out the vascular compartment, Albumin tends to bind to the acidic drugs while Globulin tends to bind with basic drugs.

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Volume of Distribution (Vd): The volume of distribution (Vd) relates the amount of drug in the body to the concentration of drug (C) in the blood. This volume does not necessarily refer to an identifiable physiological volume but rather to the fluid volume that would be required to contain the entire drug in the body at the same concentration measured in the blood:

$$(\mathbf{Vd}) = \frac{\text{Dose (mg/kg)}}{\text{Concentration mg/liter}} \text{ liter / Kg}$$

Actual volume of distribution (Vd):

The anatomic volume that is accessible to drug, e.g. total body water of 40 L.

Apparent volume of distribution (Vd):

Is a calculated value that does not correspond to an anatomical space, a drug with a large Vd (larger than 40 L) must distribute in other tissues besides body water.

Metabolism or Biotransformation: chemical transformation of drug, Alteration of drugs by the liver. Drugs can be metabolized from active to inactive or from inactive to active. Generally drugs are made more hydrophilic by the process. Liver is the principal organ of drug metabolism. Other tissues that display considerable activity include the gastrointestinal tract, the lungs, the skin, and the kidneys.

Significance of Biotransformation:

1. Change the pharmacological activity of the drug.
2. Lead to change the solubility of the drugs, so that the lipid soluble drugs will become more water soluble, and this change will enhance the excretion of drug from the body.
3. It will minimize the time of presence of the drug in the body.

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Metabolism pathways: - drug metabolism is biphasic process, drugs undergo phase I then phase II or directly phase II according to the chemical nature of the drug.

(Phase I) Oxidation, Reduction, and Hydroxylation:

Mixed-Function Oxidases, formed by microsomes made out of SER folded over on itself.

- introduce or unmask polar chemical groups therefore increase water solubility .
- mediated by cytochrome P450 enzymes .
- P450's are found in the endoplasmic reticulum or cell cystoplasm.

Cytochrome-P450 Enzyme Complex: Has four required components in order to work.

- Cytochrome-P450 Enzyme .
- Cytochrome-P450 Reductase .
- O_2 .
- NADPH: NADPH is the only energy source. No ATP is required.

Phase I enzymes perform multiple types of reactions:

1. OXIDATIVE REACTIONS: on drugs, such as Aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, S-dealkylation, N-Oxidation, S-Oxidation, Desulfuration.
2. REDUCTIVE REACTIONS: Carbamyl
3. HYDROLYTIC REACTIONS: Ester hydrolysis, Amide hydrolysis.

(Phase II) Conjugation:

- Conjugation with polar endogenous substrates e.g. glucoronic acid, glutathione.
- Increases water solubility and renal elimination.

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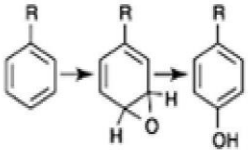
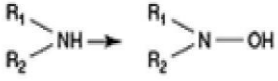
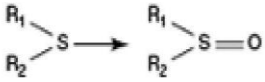
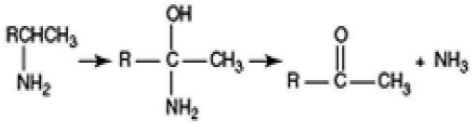
Factors which affect Biotransformation: -

1. Enzyme induction: some chemicals or drugs tends to increase amount of Metabolic enzymes which lead to increase biotransformation rate(Phenobarbitone, Glucocorticoids and Alcohol).
2. Enzyme inhibition: other chemicals or drugs tends to decrease amount of metabolic enzymes which lead to decrease biotransformation rate (Cimitidine, chloramphenicol and carbon tetrachloride.).
3. Age: in young animals slow metabolism due to slow metabolic enzymes in the liver , also in the old animals.
4. Liver diseases: also slowing the metabolism, e.g. Liver cirrhosis, parasitic infestation of liver.
5. Species variation: Equine have high rate of oxidation, also glucournidation, Ruminants have high acetylation, Cats, Geese and Fish have low Glucournidation, dog has low acetylation.

Major Reactions Involved in Drug Metabolism

	Reaction	Examples
I. *Oxidative reactions*		
N-Dealkylation	$RNHCH_3 \rightarrow RNH_2 + CH_2O$	Imipramine, diazepam, codeine, erythromycin, morphine, tamoxifen, theophylline, caffeine
O-Dealkylation	$ROCH_3 \rightarrow ROH + CH_2O$	Codeine, indomethacin, dextromethorphan
Aliphatic hydroxylation	$RCH_2CH_3 \rightarrow RCHOHCH_3$	Tolbutamide, ibuprofen, phenobarbital, meprobamate, cyclosporine, midazolam
Aromatic hydroxylation		Phenytoin, phenobarbital, propanolol, ethinyl estradiol, amphetamine, warfarin
N-Oxidation	$RNH_2 \rightarrow RNHOH$ 	Chlorpheniramine, dapsone, meperidine
S-Oxidation		Cimetidine, chlorpromazine, thioridazine, omeprazole
Deamination		Diazepam, amphetamine

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Elimination:

Removal of drug from the body .

* Routes of elimination include:

- Urine most drugs are eliminated through this route
- stool (e.g. corticosteroids from biliary system)
- lungs (e.g. general anesthetics eliminated by expiration)
- skin and mucous membranes (e.g. rifampin in tears)
- Mammary gland .

Amount of excreted drug = Amount of filtered drug + amount of active secreted drug – amount of absorbed drug.

Clearance of drug: volume of blood which cleared from drug per unit of time

CL = rate of elimination / C

Half life ($t_{½}$): time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

$$t_{½} = \frac{0.693}{Ke}$$

0.693: inverse natural log. of 2.

Ke (1/minute): constant of drug elimination, In case of drug follow the first order of excretion .

FIRST-ORDER EXCRETION: The rate of excretion of a drug is directly proportionalto its concentration.

ZERO-ORDER EXCRETION: The rate of excretion of a drug is independent of its concentration.

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The Pharmacodynamic:

The relationship between the drug concentration and effect (what the drug does to the body).

Receptor:

it's a macro molecule component of cell when bound to low concentration of drug will produce action.

Nature of receptors:

Receptors in nature may be:

1- proteins\ nicotinic receptor
2- enzymes\ $Na^{+}K^{+}$ ATPase
3- DNA
4- RNA
5- Ribosomes

Types of receptors:

1. Ligand - gated ion channels: this type of receptors is responsible or regulation of flow of ions across cell membrane. The duration of action of these receptors is very rapid (a few milliseconds), E.g. GABA - receptor, nicotinic receptor.
2. G protein coupled receptors: a single peptide linked to the G protein complex this receptor work when a drug molecule link with this complex lead to promotion of second messengers inside the cell (cAMP, phospholipase then Inositol triphosphate $IP_3$and diacylglycerol DAG) which responsible of regulation of calcium concentration within cell. E.g. norepinephrin, dopamine, serotonin and Acetylcholine receptors. The duration of action of these receptors is between several seconds to minutes.

3. Enzyme linked receptors: receptors consist of those of that have a cytosolic enzyme activity as an integral component of their structure or function, binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. The duration of action of these receptors is extended from minutes to hours. E.g. insulin hormone receptor.
4. Intracellular receptors: this type of receptors is differs from the other previous in that the receptor is entirely intracellular and, therefore, the ligand must diffuse in to the cell to interact with the receptor, e.g. steroid hormones which must enter to the cell and bind to DNA to exert its effect, The duration of action of these receptors is extend from hours to days.

Characteristic features of receptor:

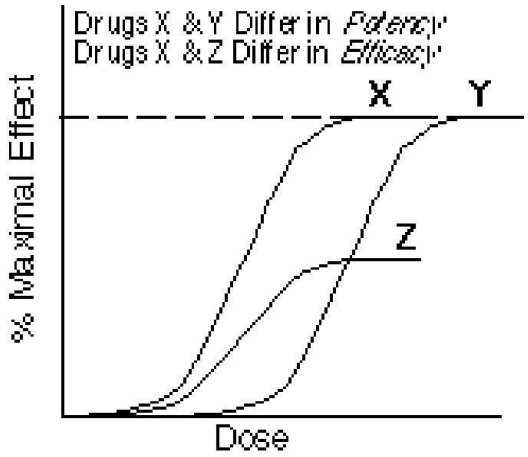
1. specific chemical structure .
2. ability of saturation .
3. irreversibility .
4. blocking by specific antagonist .

Types of drug response:

- Graded response: the response following the dose of the drug
- Quantal response (all or non response).

Potency: A potent drug induces the same response at a lower concentration.

Efficacy: The biologic response resulting from the binding of a drug to its receptor.



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- **ED50**: The drug-dosage at which 50% of the population attains the desired characteristic.
- **LD50**: Lethal-Dose-50. The drug-dose at which 50% of the population is killed from a drug.

THERAPEUTIC INDEX = LD50 / ED50

- The ratio of median lethal dose to median effective dose.
- The higher the therapeutic index, the better. That means that a higher dose is required for lethality, compared to the dose required to be effective.

- **MARGIN OF SAFETY = LD1 / ED99**

- The ratio of the dosage required to kill 1% of population, compared to the dosage that is effective in 99% of population.
- The higher the margin of safety, the better.

Agonists Have Two Main Properties

Affinity: the ability of the agonist to "bind to" the receptor

Efficacy: the ability to cause a response via the receptor interaction

e.g. the ß2-agonist (salbutamol) bind to ß2-receptors (i.e. has affinity) and result in activation of smooth muscle relaxation (ie. has efficacy)

Antagonists

have affinity (can bind to a receptor) but no efficacy

- **chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist binding to receptor • e.g. chelator agents for removal of heavy metals
- **functional antagonism**: interaction of 2 agonists that act at different receptors independent of each other but have opposite physiological effects• e.g. acetylcholine at the muscurinic receptor decreases HR, constricts pupil, stimulates intestinal motility • epinephrine at the adrenergic receptor increases HR, dilates pupil, decreases intestinal motility .

- **competitive antagonism** (most common in clinical practice)
  - antagonist acts at same receptor (i.e. binds) displacing agonist
  - antagonist binding is reversible and can be overcome

- **non-competitive antagonism**
  - irreversible binding of antagonist to receptor
  - allosteric effect: changes ability of the agonist to bind to the receptor through various mechanisms such as changing the conformation of the receptor
  - increasing concentrations of agonist cannot reverse the antagonism.

Tolerance:- decrease the action of the drug due to long persistent use.

Tachyphylaxis:- sudden decrease in the response after use of one dose.

Idosynacrasy:- unusual response to the drug.