CHAPTER

GENERAL PHARMACOLOGY

Pharmacology :-It is the science which deals with the study of drugs and its Mechanism ADR, contraindication and therapeutic uses etc

Pharmacology

↙ ↘

(1)Pharmacokinetic
♦Effect of body on drug (what does the body to the drug - Absorption, Distribution, meta bolism and excrection (ADME)

(2)Pharmacodynamic
Effect of Drug on body (giving Biological response)
♦ Related to Enzyme and Receptor
It include, action and mechanism of Drug

(1)Pharmacokinetic

Absorption- Primary site - small intestine (Basic PH-7.4)
other - stomach for acidic drug
♦Drug may be acidic or basic get absorbed by ionization (Not 100 % or Not zero)

Ionisation

↙ ↘

Ionised form (water soluble)

un ionised form (lipid soluble)
↓
can cross biological membrane
↓
get absorbed

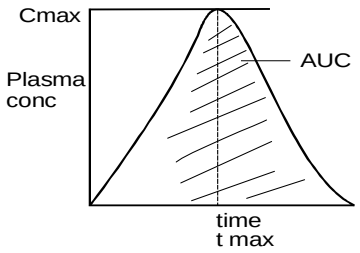
Bio availability(BA) - fraction or concentration reaches in blood circulation in unchanged form.
♦Metabolic form not counted as bioavailable amount.

Bioavailability depends on:-

(1) BA α Absorption

(2) BA $\alpha \frac{1}{\text{first pass metabolism}}$

(3) Route of Drug administration
♦ Systemic > Local route



♦ Parentral > oral
♦ IV route have 100 %

2 **Distribution -** Amount of blood distributed drug into various tissue called volume of Distribution (Vd).

$$Vd = \frac{\text{Dose Administered I.V}}{\text{Plasma concentration}}$$

$$Vd \propto \text{Lipid Solubility}$$

$$Vd \propto \frac{1}{\text{Plasma protein Binding}}$$

♦ Min Vd should be 42 L/kg .
♦ Max Vd 1300 L/kg (chloroquine with highest Vd).
♦ Vd α Plasma Half life.
♦ Vd determine loading dose.

Metabolism

♦ Most of Drug are deactivated by metabolism.
♦ **Primary site** - liver (Max enzymatic concentration).
♦ **Other**- Lungs, Adipose tissue, small intestine etc.
♦ First pass metabolism may be in small intestine, lungs ,Adipose tissue and liver.
♦ Some drug get activated from its inactivated form called prodrug.
♦ Microsomal and Non microsomal enzyme are involved in meta bolism.
♦ Microsomal enzyme can be induced or inhibited by other drugs.

Enzyme inducer

1) Enzyme inducer ↑ese metobolism, ↑ Elimination
↓ Effeet of other drug

♦ So increase dose when administered with enzyme inducer
Ex. Griseofulvin, phenytoin, Rifampicin, smoking,carbamazipine, phenobarbitone
♦ Phenobarobitone and phenytoin are CI(contra indication) in porphyria because They ↑ese porphyrin

2)Enzyme inhibitor ↓ese metabolism, slow Elimination,Predispose toxicity
Ex - MAO inhibitor, valproate, ketoconazole, cimetidine, ciprofloxacin ,Erythromycin and INH. Metronidazole, chloramphenicol etc.

3)Prodrug - Drug activated by metabolism .
♦ Biological effect related to active metabolite
Ex. ♦ All PPI
♦ All ACE inhibitor except captopril and lesinopril
♦ NSAID - Sulindac, Nebumetone
Anticancer - cyclophosphamide, Mercaptopurin, fourouracil
Anti influenza - Osaltamavir (Doc in swine flue and Bird flu)
Dipivefrine - Doc in Iron poisoning during thalasemia treatment (orphan drug)
Sulfonamide - sulfasalazine

Phase I (Non synthetic) reaction - Attachment of functional group

Ex.- oxidation, Reduction, Hydroxylation, cyclization and decyclization

♦ Drug after phase I reaction may be lipid soluble or water soluble

Phase II (synthetic) Attachment of conjugate

Ex. sulfation, methylation, acetylation, glucoronidation, glycine conjugation or other conjugation

♦ Drug after phase II reaction will be water soluble

Excretion

Primary site - kidney

- Nephron is unit of excretion
- G FR - 130 ml/min

1)Glomerular filtration - depends on plasma protein Binding and renal Blood flow.

2)Tubular reabsorption - depend on lipid solubility

3)Tubular secretion - Neither depend on lipid solubility Nor on plasma protein Binding or Renal Blood flow

Rate of Elimination

♦ **Clearance** - Rate of Elimination divided by its plsama concentration

♦ **Order of kinetic:-**

Rate of Elimination α [Plasma concentration]^{order}

1)first order kinetic (Linear kinetic)

♦ Constant fraction of drug eliminated per unit time.

♦ Clearance - constant.

♦ Half life - constant.

♦ Max. drug follow first order kinetic.

♦ Rate of elimination depend on plasma conc^{n}

2)Zero order kinetic (Non Linear kinetic)

♦ constant amount of drug eliminated per unit time

Clearance - At low conc^{n} - clearance is more

At high conc^{n} - clearance is less

Half life - At high conc^{n} - $t_{1/2}$ is more

At low conc^{n} - $t_{1/2}$ is less

♦ Always independent to plasma conc^{n}

Ex- warferrin, Aspirin, Alcohol, Theophylline, Tolbutamide and phenytoin.

(2)Pharmacodynamic

♦ Effect of drug on body.

♦ Include Action and mechanism of drug.

♦ Both enzyme and receptor are involved

(i)Receptor:-

Affinity - Abililty of drug bind or combine with receptor

Intrinsic Activity - Ability of drug to activate receptor also called Afficacy

♦ IA may be +1 to zero to +1

♦ Agonist $\rightarrow$ IA = +1 (Maximal activation)

♦ Partial Agonist $\rightarrow$ IA = zero to +1 (Submaximal activation)

♦ Antagonist → IA = zero
♦ Inverse Agonist → IA = – 1

(ii) Enzyme inhibition

↙ ↘

♦ Competitive Enzyme inhibition
- similar structure of drug and substrate
- Need active site to bind
- Inhibition can be over come by Increasing conc^{n} of substrate

♦ Non competitive Enzyme inhibition
- No similar structure of drug and substrate
- No need of active site
- Inhibition can not over come by Increasing concentration dose of substrate

Half life

Time required to reduce plasma concentration to 50 % of the original value.

$$t_{1/2} = \frac{0.693 \times vd}{clearance}$$

Half life depend on metebolism, vd, and clearance.

Therapeutic Drug monitoring (TDM)

♦ Dose Adjustment according to plsama conc^{n}
♦ More TI → drug safe
♦ Less TI (Therapeutic index) → drug may be toxic
♦ TDM done for drug those serum level and toxicity are correlated
♦ TDM required for Drugs having low therapeutic index (Digitalis, Lithium, TCA, Theophyline and tecrolemus etc
♦ T D M is not done for prodrug.

Receptor (Protein material)

1)GPCR(G protein coupled receptor)- $\alpha, \beta,$ Muscarinic $5HT_1$, $5HT_2$
2)Ionotropic - fastest acting receptor Ex. $GABA_A$, NM DA, $5HT_3$, N_M N_N
3)Enzymatic - Have two site(1) Extracellular - for drug (2) Intracellular- enzymatic (Tyrosine kinase)
Ex- Insulin, GH , Prolactin, cytokines
4)Intracellular - slowest acting
(a) Cytoplasmic - glucocorticoid, Mineralocorticoid and Vit-D
(b) Nuclear - T_3, T_4, PPAR, estrogen, progesterone and Testosterone

Route of Drug Administration

(1) Local Route:-

(A) Topical:- ♦ skin (medicated and non medicated formulation)
♦ Through Mucous Membrane
(1) Ocular (Eye)
(2) Intranasal (Nose)
(3) Otitic (Ear)
(4) GIT - Non absorbable drug like Neomycin, sucral fate, Mag hydroxide

(5) Bronchi and Lungs
(6) **Anal -** suppositories, ointment
(7) Vaginal - pesseries
(8) Urethra - vogies, jelly
(B) Deeper tissue - ♦ Intra thecal
♦ Intra articular
♦ Retro bulbur
(C) Intra arterial - for contrast media in Angiography

(2)Systemic :- Drug reaches in Blood circulation

(a) Oral - most convenient, painless
- have first pass metabolism
- show less Bioavailability

(b) Sublingual - Drug placed under the tongue
- Ex. lipid soluble drug like- Nitroglycerin, clonidine, isoprenaline and Nefidipine
- Avoid first pass metabolism

(c) Buccal - drug between gum and chick
- used for lipid soluble drug
- Ex. Lozenge

(d) Transdermal- for highly lipid soluble
Ex- Scopolamine,Nicotine and Nitroglycerin

(e) Inhalational- Drug for Asthma - Salbutamol, Ipratropium
Anaesthesia - Nitrous oxide

Parentral Route (Have More bioavailability)

IM - Angle - 90°
Muscles- gluteous maximus, Deltoid, Retus femoris
SC - Angle - 45°
- Irritant drug can not be administered.
(1)**Dermojet** - No Needle.
(2)**Pellet Implantation** - solid pellet introduced by trocher and canula.
(3)Non Biodegradable(Sialistic) and Biodegradable implant.

Intradermal-(ID) - Angle - 15-17°
-Also called intra cutaneous
-Majorly for diagnostic purpose
-Ex. BCG

Intra oseus - Drug placed in Bone Morrow

Dose

Loading dose - Therapeutic dose administered at the begining of Treatment
-Have no time interval
-May be administered in higher concentration
-Loading dose always determine by Vd

Maintenance Dose - Therapeutic dose administered with a specific time interval

-Have time interval

-Depend on clearance

Potency -Amount of drug needed to produce the respones.

-Lower dose produce same response will be more potent

-Those require Large dose for same response will be Less potent

Effective Dose (ED_{50}) - Dose that produce 50 % (Half) response of its maximum.

-More ED_{50} lower the potency

Lethal Dose (LD_{50}) - Dose that result 50 % death of animal after receiving.

-More LD_{50} , safer the drug

Therapeutic Index $(TI) = \frac{LD_{50}}{ED_{50}}$

-TI is a Measure of safety. Drug have More TI are safer where as Low TI of Drug show toxicity.

ADR (Adverse drug reaction/adverse effect)

Pharmacovigillance - Detection, Assesment, Prevention and under stading of Adverse effect.

(A) Predictable ADR - These are Dose related adverse effect.

(1) **Side Effect** - Related to therapeutic dose.

(2) **Secondary Effect** - Related to primary Mechanism of Drug - Ex. super infection.

(3)**Toxic effect**-Related to over dose or prolong used of drug.

(4) **Tolerance** -Related to prolong used.

(5) **Photo toxicity**

(B) Unpredictable ADR - Least related to Dose

Allergy - Change in Immune system (I_gE),

Idiosyncracy - change in genetic system

♦National pharmacovigillance programme was started november 2004 under CDSCO

Placebo (Dummy drug)

- **Single Blind** - Clinician know, patient don't know
- **Double Blind** - Both Clinician and patient don't know about Drug

Orphan Drug

-Orphan drug act - 1983

-Drug that is used in rare disease or disorder called orphan drug

Ex. N-Acetylcysteine in PCM poisoning,

Defevefrone - in Thalacemia patient