PHARMACOLOGY-I

UNIT 2 NOTES

PHARMACODYNAMICS

- RECEPTORS
- DOSE RESPONSE RELATIONSHIP
- THERAPEUTIC INDEX
- COMBINED EFFECT OF DRUGS
- ADVERSE DRUG REACTIONS
- DRUG INTERACTIONS
- DRUGS DISCOVERRY
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PHARMACODYNAMICS

- Pharmacodynamics is the study of actions of drugs on the body and their mechanism of action.
- In one words it is the study of what drug does to the body.
- It examines how a drug interacts with its target sites, such as receptors and enzymes, and how these interactions lead to changes in physiological processes and therapeutic effects.

MECHANISM OF DRUG ACTION

The Drugs shows their mechanism of action mainly by two types:

① Receptor Mediated
② Non- Receptor Mediated

NON - RECEPTOR MEDIATED

The non- receptor mediated action includes:

- By Physical Action
- By Chemical Action
- Through Enzymes
- Through Ion Channels
- Through Transpooters
- Through Antibody Production

① By Physical Action

The drugs can show their action on the basis of physical properties:

- Osmosis : Mannitol
- Adsorption : Activated Charcoal in poisoning
- Radioactivity : ^{131}I (In Hyperthyroidism)
- Mass of Drug : Bulk Laxatives

② By Chemical Action

Drug may act by chemical reactions :

- Antacids : Neutralise Gastric Acids
- Chelating Agents : Dimercaprol in Arsenic & Mercury Poisoning
- Oxidising Agents : Potassium Permanganate

③ Through Enzymes

- Drugs can influence enzymes in various ways to show their action :
- Here are primary mechanism :

Enzyme Activation :
- Some drugs act as enzyme activators, increasing enzymes activity.
- Allopurinol

Enzyme Inhibition :
- Many drugs work by inhibiting specific enzymes. This inhibition can be of two types
  ① Competitive : Captopril, Neostigmine
  ② Non-Competitive : Acetazolamide

④ Through Ion Channels

Drugs may intefere with the movement of ions across specific channels either by opening or closing them.

- Voltage Gated Ion Channel : Local Anaesthetics

⑤ Through Transporters

- Drugs may act by blocking or inhibiting the movement of transporters, symporters or antiporters.
- Selective Serotonin Reuptake Inhibition (SSRI).

⑥ Through Antibody Production

- Drugs can also show their action through Antibody, typically Monoclonal Antibodies
- Vaccines

Receptor Mediated Mechanism

- In Receptor mediated mechanism, drug exerts their effect by binding to specific receptor on the surface or within cell.
- Most of the drugs shows their effect by this mechanism.
- The drug- receptor interaction triggeres a series of biochemical events that lead to a physiological response.
- The intensity of pharmacological effect is directly proportional to number of receptor occupied.

Receptors

- Receptors are macromolecules, present either on the cell surface, crytoplasm or in the nucleus, from which the drug binds and interacts to produce cellular changes.
- Receptors are mostly proteins

Drug + Receptor ⟷ Drug- Receptor Complex → Response

Classification Of Receptors

The receptors are of following types:

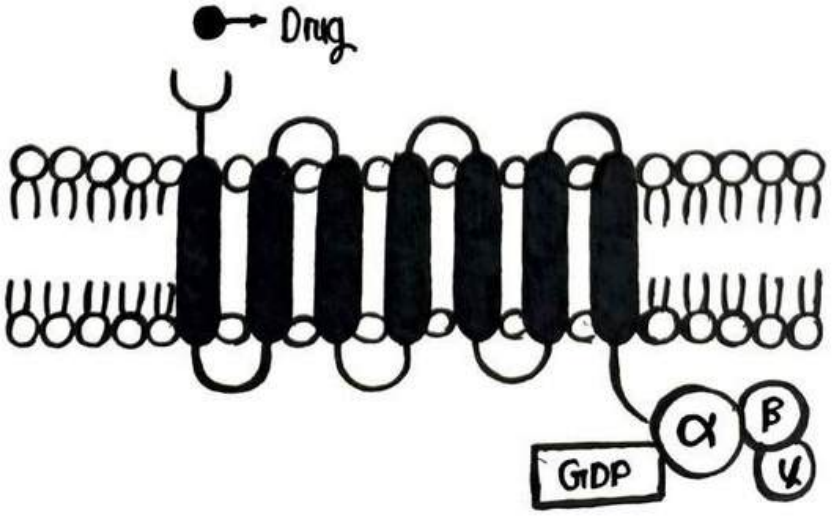
① G- Protein Coupled Receptor
② Ion Channel Receptors
③ JAK- STAT Binding Receptor
④ Enzymatic Receptors
⑤ Nuclear Receptors

G - Protein Coupled Receptors

- G - Protein Coupled Receptors are a large family of cell membrane receptors that plays a crucial role in cellular signal transduction.
- They are present on ~~ff~~ surface of cell membrane.
- They are also known as Metabotropic Receptors, Heptahelical Receptor and Serpentine Receptors
- G - Protein are membrane proteins and have three subunits (α, β, γ) called heterotrimeric along with GDP.
- G - Proteins act as Signal Transducers.
- The GPCR act by second messenger activation mechanism.
- The second messengers include cAMP, IP_3., DAG, Ca^{++} & cGMP.
- When a ligand binds to GPCR it activates either Adenyl Cyclase or Phospholipase C to generate respective second messengers.

Types Of G - Protein

① G_s : Adenyl Cyclase Activation : cAMP ↑
② G_i : Adenyl Cyclase Inhibition : cAMP ↓
③ G_o : Ca^{2+} Channel Inhibition :
④ G_q : Phospholipase C Activation : IP_3 ↑, DAG ↑



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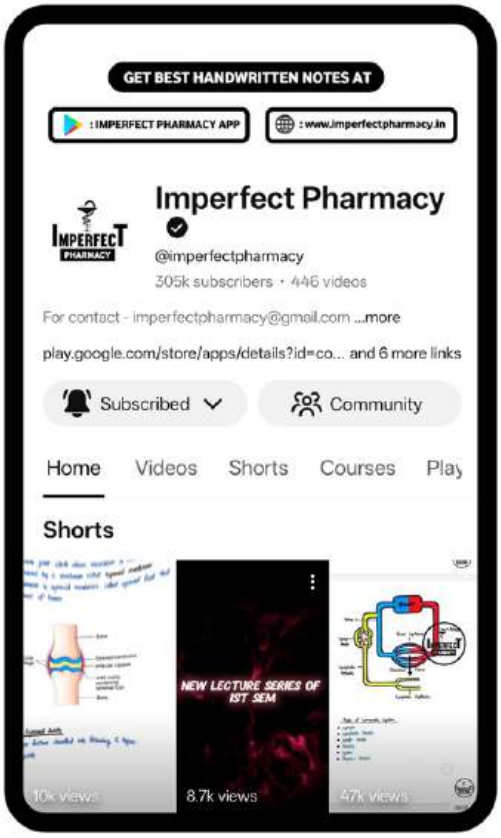

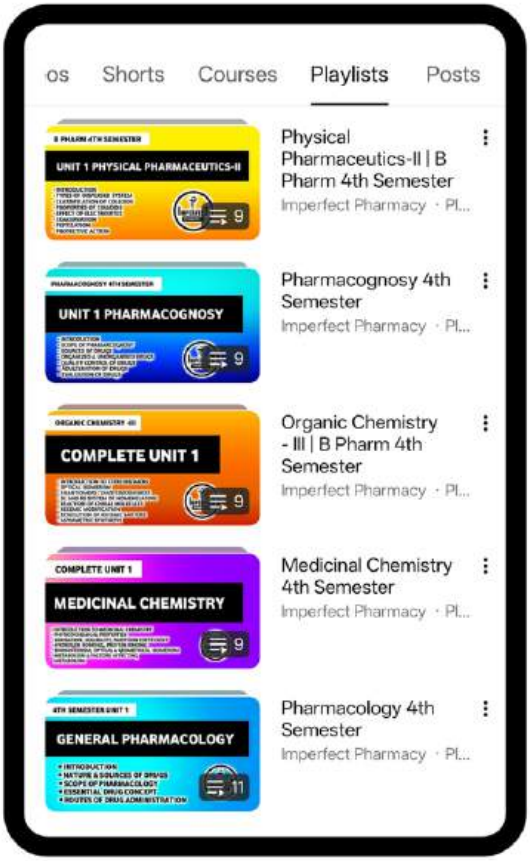

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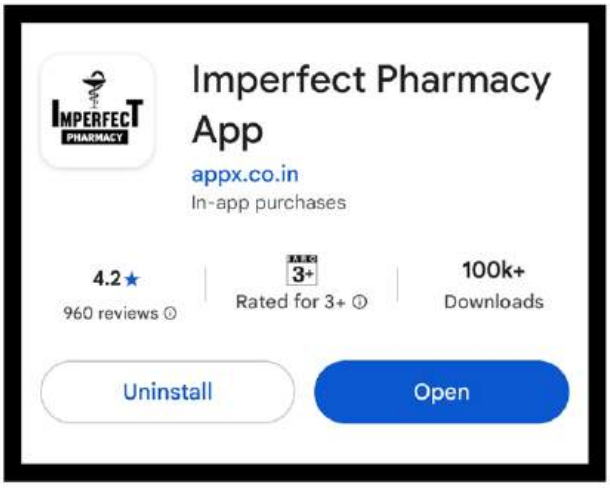


- G-Protein Coupled Receptor controls cell function by 3 major pathways :

① Adenyl Cyclase - cAMP Pathway
② Phospholipase C : IP_3 - DAG Pathway
③ Channel Regulation

① Adenyl Cyclase [AC] : cAMP Pathway

- It is activated Gs & inhibited by Gi
- Activation of Adenyl Cyclase result in increased synthesis and intracellular accumulation of cAMP.
- cAMP acts through Protein kinase which phosphorylate and alters the function of many enzyme, ion channels and structured proteins.

Activation of AC → cAMP ↑ → Protein kinase Activation

↓

Phosphorylation of Protein enzyme, ion channel & structural proteins

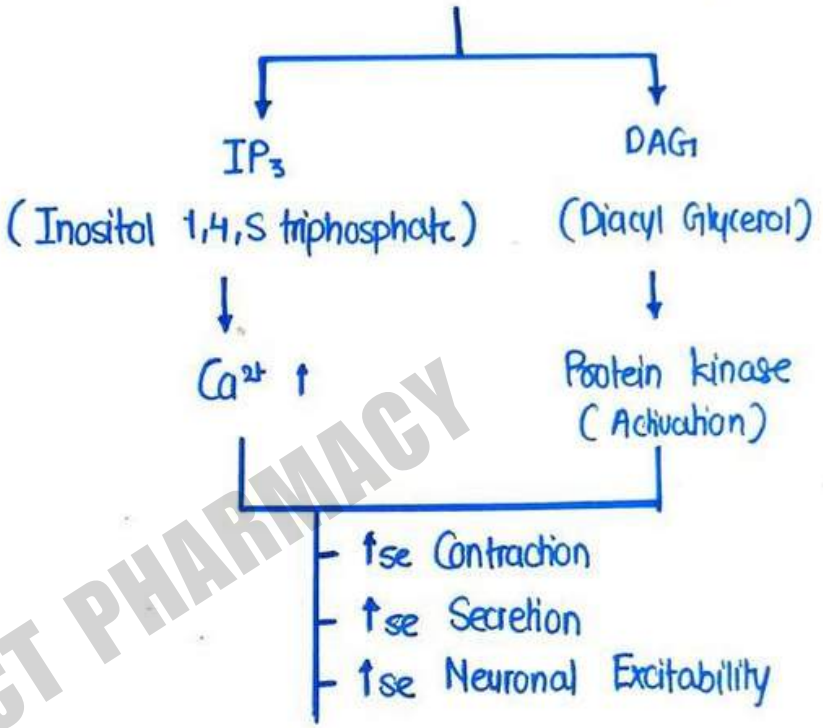
↓

Functions

- Heart Contractibility ↑
- Smooth Muscles Relaxation
- Liver (Glycogenolysis)
- Adipose Tissue (Lipolysis)

② Phospholipase C : IP_3 DAG Pathway

- It is activated by G_q protein
- Activation of Phospholipase C ⟶ Hydrolyses Membrane Phospholipid



③ Ion Channel Regulation

- Activation of G-Protein can open and close specific ion channels
- It doesn't involve any second messenger.
- ↑ Ca^{2+} : Adrenergic (β_1)
- ↑ K^+ : Adrenergic (α_2), Muscuranic (M_2)

ION - CHANNEL RECEPTORS

- It is also known as Ligand Gated Ion Channels or Ionotropic Receptors.
- This drug binds directly to the receptor located on an ion channel without mediated by G- Protein.
- These types of receptors are fastest acting receptors.
- Binding of Drug To Ionotropic Receptor → Opens the ion channel (Na, k, Ca^{2+}, Cl) → Flow of Ions → Hyperpolarization / Depolarization → Tissue Response
- e.g. GABA Receptors, NMDA Receptors

ENZYMATIC RECEPTORS

- These receptors are directly linked tyrosine kinase.
- Receptor binding domain present in extracellular site.
- The intracellular site has enzymatic activity.
- Example
  - Prolactin
  - Insulin
  - Growth Hormones
  - Cytokines

NUCLEAR RECEPTOR

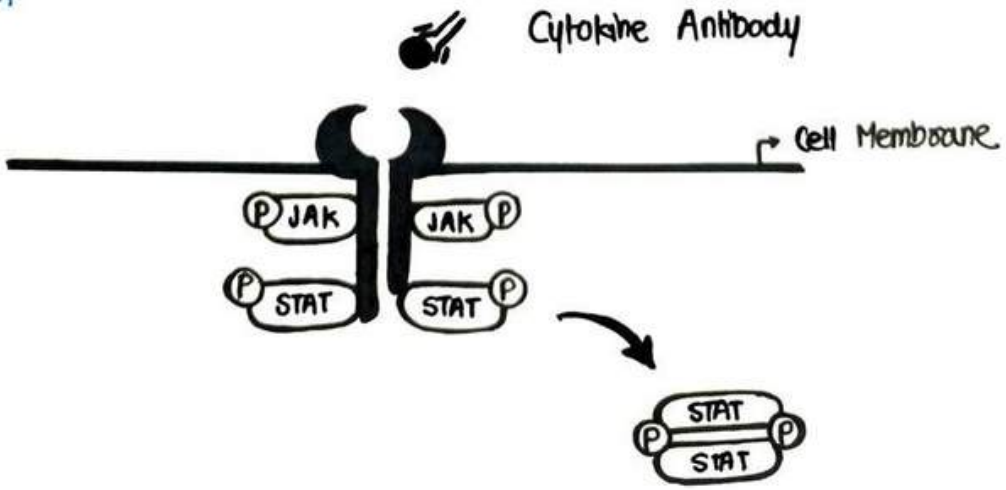
- This type of receptors are slowest acting.
- Only lipid soluble drugs can act on it.
- If drugs binds with nuclear receptor, then they bind with
- DNA and acts on translation, transcription etc.
- Two major types of nuclear receptors are :

① Cytoplasmic receptor
② Nuclear Receptor

JAK-STAT BINDING RECEPTOR

- The Jak-stat (Janus kinase-signal transducer & activator of transcription) signalling pathway transmits information from chemical signals outside the cell, that causes DNA transcription and activity of cell.
- It consist of 3 main components

① Receptor
② JAK
③ STAT



① JAK

- JAK stands for 'Janus kinase'
- It is a type of enzyme that helps start a signal when a molecule (like hormone or drug) binds to the receptor.

② STAT

- STAT stands for 'Signal Transducer & Activator of Transcription'.
- It is a protein that carries the signal into the cell's nucleus, where it turn specific genes on or off.

③ Receptors

- A specialized structure on cell's surface that recognizes & capture signalling molecule, activating JAK & STAT.

PATHWAY OF JAK-STAT RECEPTOR

Signalling Molecule Attaches To JAK-STAT Receptor

↓

Activated JAK

↓

Phosphorylation Of Tyrosine Residues

↓

Addition of STAT

↓

Phosphorylation Of STAT By JAK

↓

Dimerisation Of STAT

↓

Cellular Responses

FACTORS AFFECTING DRUG ACTION

Factors affecting drug action can be broadly categorized into :

① Physiological Factors
② Pharmacokinetic Factors
③ Drug-Related Factors
④ Environmental Factors

① PHYSIOLOGICAL FACTORS

ⓐ Age : • Babies and Young children have immature organs, so they process drugs slowly, which can lead to stronger effect or side effects.
• Older adults may have weaker liver & kidney function, so drugs stays in their body for longer duration, increasing the risk of side effects.

ⓑ Gender : • Men & Women process drugs differently due to hormones, body fat & muscle composition.

ⓒ Body Weight : • Heavier people may need higher doses of some drugs.
• Fat-soluble drugs stay longer in people with more body fat.

ⓓ Genetics : • Some people naturally breakdown drugs faster or slower due to inherited traits.

ⓔ Health Problems : • Liver & kidneys are organs that help remove drugs from body, if they aren't working well, drugs stays longer in body, increasing side effects.

② PHARMACOKINETIC FACTORS

ⓐ Absorption :
- IV drugs go directly into the bloodstream & work quickly
- Some drugs work better with food (fat soluble vitamins)
- Some drugs work best on an empty stomach.

ⓑ Distribution :
- Drugs like Warfarin bind to albumin leads to increase DOA & may leads to toxicity
- Barriers like BBB limits the entry of certain drugs into the brain, affecting drug efficacy in neurological disorders.

ⓒ Metabolism :
- The liver is the main organ that metabolizes drugs. Some drugs are broken down quickly, so they need frequent doses

ⓓ Excretion :
- The kidneys filter out drug through urine. If kidneys are not working well, the drug stays in the body longer.

③ DRUG RELATED FACTORS

ⓐ Dose & Strength :
- A higher dose leads to stronger effects but also a higher risk of side effects.

ⓑ Route of Administration :
- IV : Works Instantly.
- Oral : Slower as it goes through digestion
- Inhaler : Acts quickly in lungs.
- Topical : Work on specific area.

© Drug Interactions :
- Some drugs enhance each other. Example : Alcohol + sleeping pills = extreme drowsiness.
- Some drugs cancel out each other : Some antibiotics make birth control pills less effective

④ ENVIRONMENTAL FACTORS

ⓐ Diet & Nutrition :
- A healthy diet supports good drug metabolism.
- Smoking speeds up drug metabolism.
  Deficiencies (like low protein or vitamins) can affect how drugs work.

DOSE RESPONSE RELATIONSHIP

- The dose - response relationship describes how the amount of drug (dose) affects body's response.
- It helps in understanding how much of a drug is need to achieve the desired effect while avoiding toxicity & side effect.

KEY COMPONENTS

① Dose : The quantity of drug administered.

② Response : The biological reaction which could be beneficial or harmful.

③ Toxic Dose : A high dose that causes harmful or dangerous effect.

TYPES OF DOSE RESPONSE RELATIONSHIP

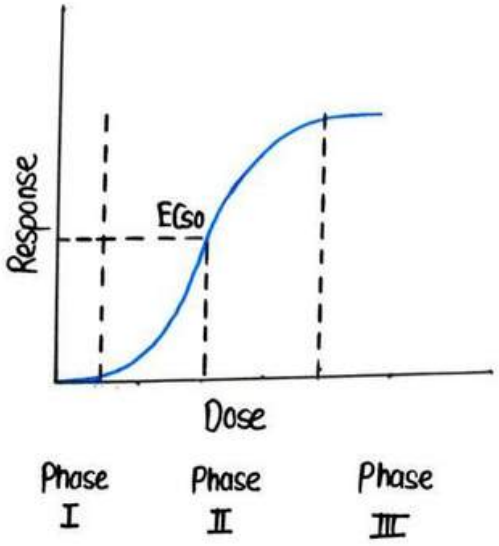
① Graded Dose Response Relationship

- In this response increases gradually as the dose increases.
- Example : A painkiller provides mid relief at a low dose, stronger relief at a moderate dose & full pain relief at a high dose.

② Quantal Dose - Response Relationship

- Instead of a gradual increase, it measures whether a response occurs or not in a population.
- Example : A sleeping pill might work for some people at 5 mg, for some at 10 mg & for almost everyone at 20 mg.

Dose - Response Curve



- **Phase I**

  The dose is too low to cause any response

- **Phase II**

  The dose increases & the desired effect appear

- **Phase III**

  Further increase in dose does not increase beneficial effect.

EC50

- EC50 stands for Effective Concentration 50%.
- It is the dose that produces 50% of maximum response.

THERAPEUTIC INDEX

- The Therapeutic Index (TI) is a quantitative measure that compares the safety & efficacy of drug.
- It is defined as ratio of dose of dose of a drug that causes Toxicity to the dose that produces a therapeutic effect.
- Mathematically, it is expressed as :

$$TI = \frac{TD_{50}}{ED_{50}}$$

Here,

- TD_{50} (Toxic Dose 50%) : The dose at which 50% of the population experiences toxic effects.
- ED_{50} (Effective Dose 50%) : The dose at which 50% of the population expeniences the desired therapeutic effect.

TYPES OF THERAPEUTIC INDEX

① High TI Drugs : These drugs have a large difference between the therapeutic & toxic doses, making them safer.
Example : Penicillin

② Low TI Drugs : These drugs have a narrow margin of safety, requiring careful monitoring.
Example : Warfarin, Digoxin.

COMBINED EFFECT OF DRUGS

If two or more drugs administered simultaneously, they can either show synergism or antagonism.

① SYNERGISM

- It is the phenomenon in which action of one drug is facilitated or raised by other drugs.
- It can be of two types

ⓐ Additive :
- In this two drugs with similar MOA are combined & their effects sum up.
- Effect of A + B = Effect of A + Effect of B
- Example : Aspirin + Paracetamol for pain relief

ⓑ Supra - Additive :
- Combinations produce greater effect than the individual effects of each component.
- Effect of A + B > Effect of A + Effect of B.
- Example : Sulfamethoxazole + Trimethoprim (antibiotics)

② ANTAGONISM

- Antagonism is a type of drug interaction where the effect of 1 drug is reduced or completely blocked by another drug.
- It is of following types:

ⓐ Chemical Antagonism
ⓑ Pharmacokinetic Antagonism
ⓒ Physiological Antagonism
ⓓ Competitive Antagonism
ⓔ Non- competitive Antagonism

ⓐ Chemical Antagonism :
- One drug interacts chemically with another to neutralize its effect.
- Example : Protamine Sulfate neutralizes the anticoagulant effect of heparin.

ⓑ Pharmacokinetic Antagonism :
- One drug affect ADME of another reducing its concentration.
- Example : Rifampicin induces liver enzymes that increases the metabolism of warfarin, reducing its effect.

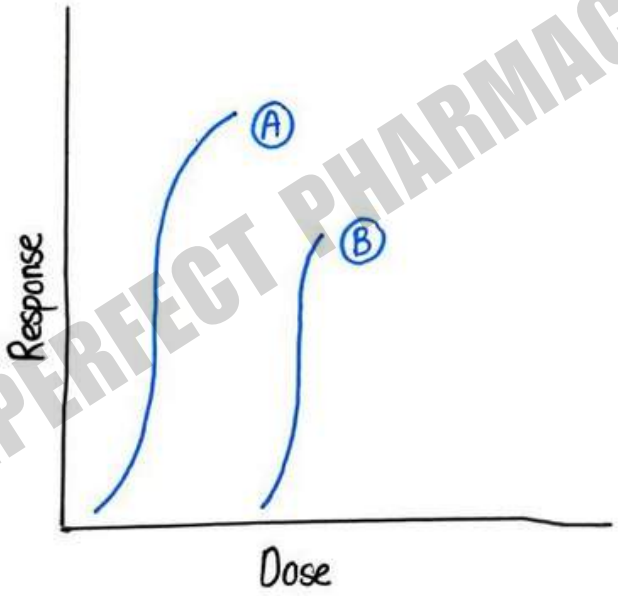
ⓒ Physiological Antagonism :
- Two drugs act on different receptor or pathways to produce opposite physiological effects.
- Example : Adrenaline (increases blood pressure) & histamine (lowers blood pressure) have opposing actions.

ⓓ Competitive Antagonism :
- Two drugs compete for the same receptor, and the antagonist prevent the agonist from binding.
- Example : Naloxone competes with opoids (Morphine) at opoid receptors to reverse overdose effect.

ⓔ Non- Competitive Antagonism :
- The antagonist binds to different site on receptor or alters the receptor structure, making it non responsive to agonist
- Example : ketamine blocks NMDA receptors preventing the action of glutamate.

EFFICACY

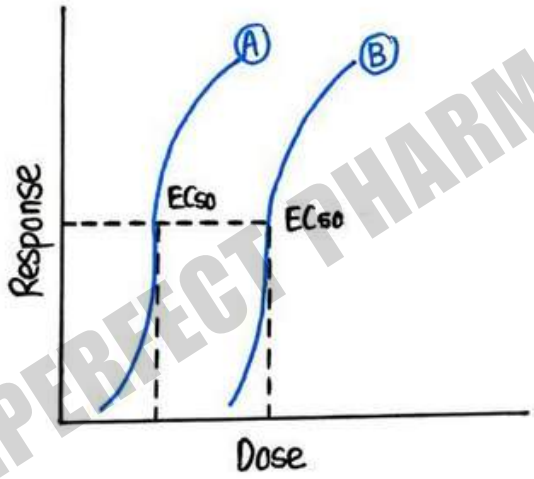
- Efficacy refers to the maximum therapeutic effect a drug can achieve. regardless of the dose.
- It indicates how well a drug activates its target receptor or biological pathway to produce the desired response.
- A drug with high efficacy produces a strong response even at low or moderate doses.
- In dose response - curve, efficacy is represented by maximum height (Emax) of the curve.



- In the above graph drug A is more efficacious than B as curve of A has more height compare to B.

POTENCY

- Potency refers to the amount of drug required to produce a given effect.
- It is determined by the dose needed to achieve 50% of the drug's maximum effect (EC_{50}).
- A drug with high potency produces the desired effect at a lower dose.
- On a dose-response curve, potency is determined by the position of the curve along the X-axis — a more leftward curve means higher potency.



- In the above graph drug A is more potent than B as it has more leftward curve

Adverse Drug Reactions

- Adverse Drug Reactions are harmful or unintended responses to a medication that occur at normal doses used for treatment, diagnosis or prevention of disease.
- These reactions can range from mild (like nausea or rash) to severe (such as organ damage or life-threatening allergic reactions.

Types Of Adverse Drug Reactions

① Type A (Augmented)

- It is common, predictable & dose related
- It is caused by drug's known pharmacological effects.
- Example: Bleeding from warfarin, hypoglycemia from Insulin.

② Type B (Bizarre)

- It is less common (rare), unpredictable & not dose related.
- Often due to allergies or genetic factors.
- Example: Anaphylaxis from Penicillin.

③ Type C (Chronic)

- Associated with long term use of a drug.
- Example: Adrenal suppression with long term corticosteroids.

④ Type D (Delayed)

- Appear after some time, even after stopping the drug.
- Example: Cancer caused by Chemotherapy Drugs.

⑤ Type E (End Of Use)

- It occurs when a drug is suddenly stopped (withdrawl).
- Example: Seizures after stopping Benzodiazepines

⑥ Type F (Failure)

- Lack of Effectiveness of the Drug.
- It occurs often due to drug interactions or incorrect dosing.
- Example: Antibiotic resistance leading to treatment failure.

DRUG INTERACTIONS

- When two or more drugs are taken together, they can interact in ways that affect their effectiveness & safety.
- These interactions can be either :

① Pharmacokinetic

② Pharmacodynamic

① PHARMACOKINETIC DRUG INTERACTION

- A Pharmacokinetic drug interaction occurs when one drug affects the absorption, distribution, metabolism or excretion of another drug, altering its concentration in the body.
- This can lead to increased toxicity or reduced effectiveness of a drug.

ⓐ Absorption :
- Some drugs can increase or decrease the absorption of another drug.
- Example : Antacids containing calcium, magnesium or aluminium can bind with certain antibiotics (e.g. tetracyclines) and reduce their absorption, making them less effective.

ⓑ Distribution :
- Drugs bind to proteins (e.g. albumin) in the blood.
- If two drugs compete for the same binding site,
- it can increase the free drug levels, leading to toxicity.
- Example : Warfarin (a blood thinner) and Aspirin both bind to albumin. when taken together, Aspirin can displace Warfarin, leading to an increased risk of bleeding.

© Metabolism :
- The liver uses enzymes to metabolize drugs.
- Some drugs can inhibit or induce these enzymes, changing how fast another drug is broken down
- Example : Grapefruit juice inhibits CYP3A4 enzymes, slowing the metabolism of statins (cholesterol-lowering drugs), leading to high drug levels & potential toxicity.

ⓓ Excretion :
- Some drugs affect kidney function, altering how drug is excreted.
- Example : Probenecid (used for gout) reduces the excretion of penicillin, leading to higher penicillin levels in the body, which may be beneficial in some cases.

② PHARMACODYNAMIC DRUG INTERACTION

- A Pharmacodynamic drug interaction occurs when two drugs affect the same biological target or pathway, leading to additive, synergistic or antagonistic effects.

PHARMACOVIGILLANCE

- Pharmacovigillance is the science and activities related to detection, assessment, understanding and prevention of adverse effect or any other drug related problems.
- Its primary goal is to improve patients safety and providing maximum therapeutic effect.
- This involves monitoring and analyzing data from various sources including clinical trials and post marketing reports to identify and manage potential risks associated with medications.

NEW DRUG DEVELOPMENT

- From the synthesis / identification of a molecule to marketing, a new drug take at least 10-20 years and it is very costly.
- There are following stages in a new drug development:
- Synthesis / Isolation of Compounds
- Pre- Clinical Trials
- Permission for Clinical Trials
- Pharmaceutical formulation, standardization of chemical
- Clinical Trials (Phase I, II, III)
- Review & Grant of Marketing Permission.
- Post Marketing Surveillance (Phase IV)

Pre Clinical Trials

- Pre clinical trials are initial phase of testing a new drug or treatment before it is tested in humans.
- This phase involves :

① Laboratory Research
② Animal Testing

① Laboratory Research

- Scientist conduct experiments using cell cultures or tissue samples to investigate the biological effects and mechanism of the new treatment.
- This helps identify potential benifits and risks.

② Animal Testing

- The treatment is tested on animals to assess its safety, efficacy and pharmacokinetics
- This step helps evaluate the potential for harmful side effects and determine the appropriate dosage.

Clinical Trials

- Clinical Trials are research studies conducted with human participants to evaluate the safety, efficacy and potential side effects of new drugs, treatment or medical services
- Clinical trials are simply perform in Humans.

PHASES OF CLINICAL TRIALS

It consist of five phases :

① Phase 0
② Phase 1
③ Phase 2
④ Phase 3
⑤ Phase 4

① PHASE 0

- It is also known as microdosing phase.
- It is an early stage of clinical research designed to gather preliminary data on how a new drug behaves in the human body.
- It is performed in very small group of participants.

② PHASE 1

- It determines the metabolic and pharmacodynamic effect of drugs.
- It is performed in 20-100 healthy persons.
- It evaluates safety of drug

③ PHASE 2

- It focuses on establishment of therapeutic efficacy & dose range
- It evaluates the efficacy of drug
- It is performed in patients (who have the disease that the drug is expected to treat)
- 100 - 300 patients.
- Duration : 6 months to several years.

④ PHASE 3

- It focuses on safety, tolerability and possible drug interactions, associated on a wider scale.
- It is a Therapeutic Confirmatory Trial.
- Performed in 100s to thousands of patients.
- It takes about 3-5 years

⑤ PHASE 4

- It is also known as Post Marketing Surveillance.
- It involves ongoing monitoring and assessment after the drug is approved & available to the public
- It focuses on long term effects & overall impact

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