UNIT-2

Pharmacodynamics

In the previous unit, we studied pharmaco-kinetics and in that we saw that what does the body do to the drug.

In pharmacodynamics, we study about "what does drug do to the body", e.i., the drug's effect on body.

The drug should be of maximum effectiveness and with minimum toxicity.

Drug action → process by which the drug induce any change in already existing physiological function of living organisms.

Drug effect → series of changes that occur after the drug action.

Principles of Drug Action

Drugs do not produce or impart any new functions to the systems, organ or cell of the body, they only alter the ongoing functions in the body.

There are few types of drug action:

(1) Stimulation → stimulation means to increase the function of any specialized organ. For example, in case of fear or fight, adrenaline gets secreted and heart rate increases which give fight and flight response.

(2) Depression → depression means the reduction in specialised activity of an organ or cell in the body.

For example, Barbiturates and benzodiazepine depress the CNS. Similarly, Omeprazole reduce gastric acid secretion.

(3) Irritation → Few drugs irritate the site of its action and produce effect.
For example, Senna used in constipation irritate the intestine and treat it. Similarly, balm, in case of headache will irritate the forehead and gives relief from pain.

(4) Replacement → when a deficiency of a hormone or any other biochemical substance in the body occurs, then it is given to the body from outside.
For example, insulin in case of insulin-dependent diabetes or iron in case of anemia.

(5) Cytotoxic action → when there is entry of a parasite, they needs to be killed by cytotoxic drugs without affecting the body's cells.
Examples → anti-microbial drugs.

Mechanism of Drug Action

Mechanism of action involves the complete process of how the drug shows its effects.
only a few drugs are capable of producing effect simply by their physical and chemical properties:

- Physical action → a physical property of the drug is responsible for its action. For example,
  - Absorptive properties:- activated charcoal can absorb poisonous substances.
- Chemical actions → the chemical property of drug is responsible for its action. For example,
  - Antacids are known for neutralizing acidic pH.
  - Chelating agents (EDTA), anti-coagulants (calcium citrate), they all use their chemical properties to induce the therapeutic effect.

Majority of drugs produce their effects by interacting with a target molecule which is usually a protein.

Functionals proteins that are targets of drug action can be grouped into 4 major categories:

- Enzymes
- Ion Channels
- Transporters
- Receptors

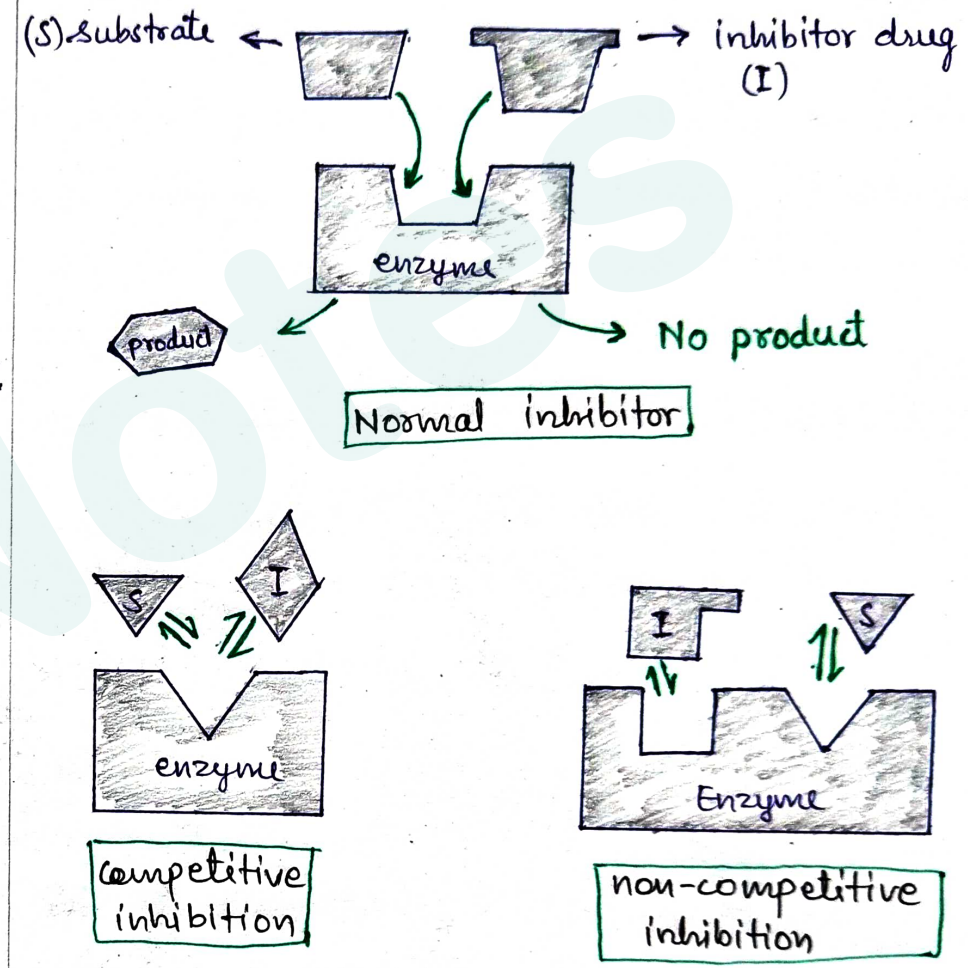
Enzymes

Almost all biological reactions are carried out under the influence of enzymes.

Enzymes are either inhibited or induced by drugs.

- Enzyme inhibition →

Mode of action of drug involves selective inhibition of a particular enzyme. Such inhibition may be competitive or non-competitive.



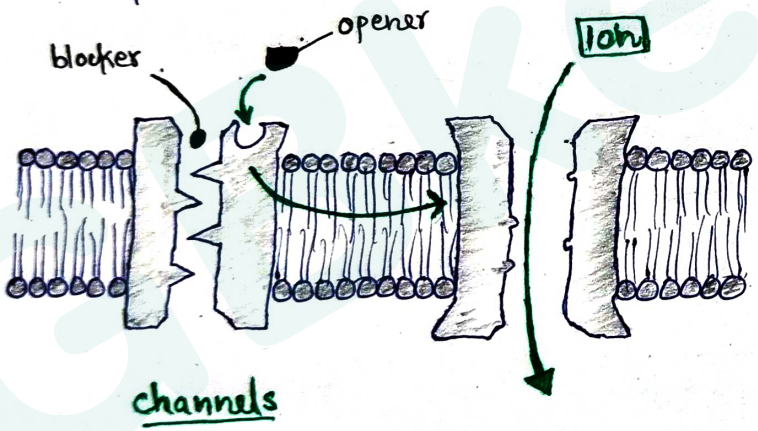
- competitive inhibition :- when the active site of an enzyme is occupied by a substance (drug) other than the substrate of that enzyme. Its activity is inhibited.

substrate → it is the substance on which the enzyme acts.

- Non-competitive inhibition :- the inhibitor does not bind to the enzyme at its active site but to a secondary site (allosteric site). Thus, inhibit the binding of substrate.

Ion Channels

Ion channels are pore forming membrane proteins that allow ions to pass through the channel pore.

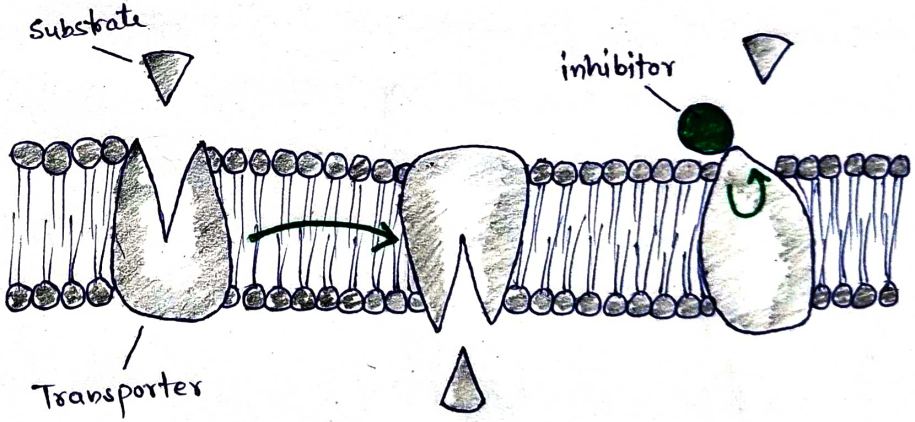


Drugs can affect the movement of ions across the cell membrane. Ex- Quinidine blocks myocardial Na^+ channels.

Transporters

several substrates are translocated across the membrane by binding to specific transporters (carriers) via either facilitated diffusion in the direction of concentration gradient or pump the ions against the concentration gradient.

Many drugs produce their action by directly interacting with the solute carrier (transporter proteins) to inhibit the transport of ions.



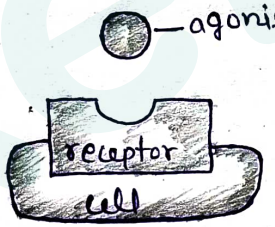
Receptors

Receptors are the binding sites for drugs that recognize the signalling and initiate the response to it. Receptors are present either on surface of cell or within the cytoplasm. Receptors, generally have no other function.

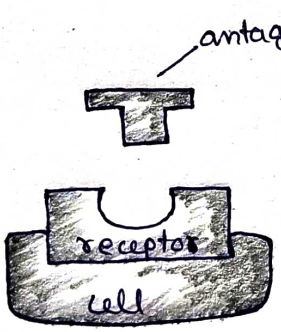
Drugs bind to receptors either to activate them or to inactivate them depending on which type of drug binds to it.

agonist → a drug which activates a receptor to produce an effect similar to that of the normal molecule that binds in the body.

antagonist → an agent or drug which prevents the action of an agonist on a receptor and eventually its response, but does not have any effect of its own.



Full activation



No activation

Receptor Theories

A receptor is the specific chemical constituent of the cell with which a drug interacts to produce its pharmacological effects.

Drug + Receptor → Drug-Receptor Complex
↳ Drug Response

1. Occupation Theory

The occupancy theory was given by Gaddum and Clark.

It states that " the intensity of pharmacological effect is directly proportional to the number of receptors occupied by the drug".

It means that maximum response will occur when all the receptors are occupied.

2. Induced-Fit Theory

This theory was given by Koshland.

→ According to this theory, the receptor need not necessarily exist in the appropriate conformation (shape) required to bind drug.

→ As the drug approaches the receptor, a conformational change in receptor could be responsible for initiation of biological response.

→ According to this theory, the receptor is elastic and could return to its original conformation or shape after the drug product was released.

→ According to the theory:

- agonist would induce conformational change in response.
- antagonist would bind without a conformational change.
- partial agonist → partial conformational change.

3. Rate Theory

This theory was given by Paton.

According to this theory, "the response is proportional to the rate of drug-receptor complex formation".

It means that the effect produced by drug molecules depends on how fast the drug interacts with the receptors.

→ In case of agonists, the rates of both association and dissociation from the receptor are fast.

→ Antagonist

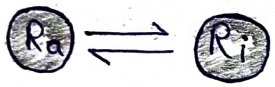
association- fast
dissociation- slow

→ Partial agonists

intermediate drug-receptor complex dissociation rates.

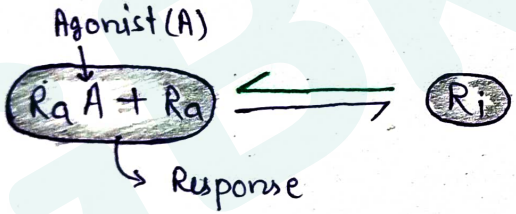
4. Two state Model For Receptor Activation

This theory postulates that, "a receptor exists in two distinct states: Ra (active state) and Ri inactive state, which are in equillibrium with each other.

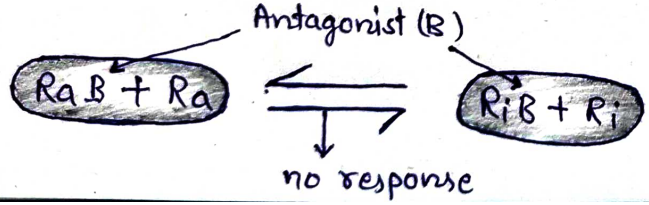


(Resting equillibrium)

→ when an agonist interacts with the receptor at equillibrium, Ra-receptor state predominates and equillibrium shifts towards Ra.



→ A competitive antagonist have equal affinity towards Ra and Ri. Equillibrium is maintained.



Classification of Receptors

The drugs can act by binding to various types of receptors:

1) G-protein coupled receptor (GPCR)
2) Ion-channel receptor
3) Enzyme linked receptor
4) Transmembrane JAK-STAT binding receptor
5) Receptor that regulate transcription factors.

Regulation of Receptors

Receptors exist in dynamic state and their number and efficacy is changed by the level of ongoing activity. On this basis, regulation may be up regulation or down regulation.

Down Regulation→ prolonged use of agonist

→ decrease in receptor number and receptor sensitivity

→ Therefore, decreased drug effect.

Up regulation → prolonged use of antagonist.

→ increase in receptor number and receptor sensitivity.

→ Therefore, decreased drug effect.

Drug-Receptor Interactions

Interactions involved in the drug-receptor complex are same forces experienced by all interacting organic molecules.

These include: covalent bonding, electrostatic ionic bonding, ion-dipole and dipole-dipole interactions, hydrogen bonding, charge-transfer, hydrogen bonding and van der Waals interaction.

Signal Transduction Mechanism

When the signaling molecule (drug in this case) binds the receptor, it changes the receptor protein in some way. This change initiates the process of transduction. Signal transduction is usually a pathway of several steps by which receptor's activation results in its response.

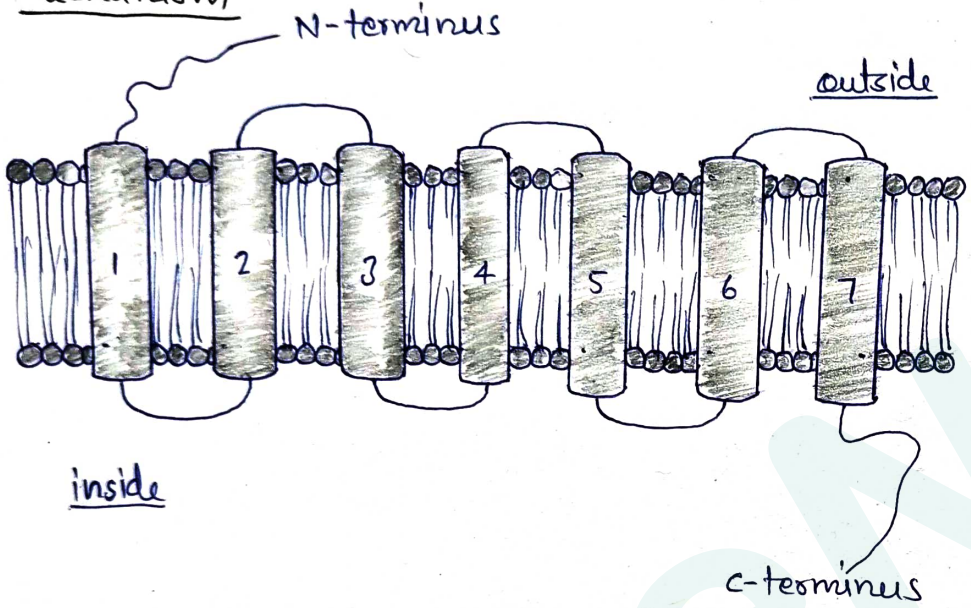
We will see the transduction mechanism in types of receptors.

1. G-protein coupled Receptor (GPCR)

GPCR protein located in the cell membrane that binds to substances and transmits signals from these substances to an intracellular molecule called G-protein (Gunine nucleotide-binding protein).

→ GPCRs are found in the cell membranes, some examples of GPCRs include beta-adrenergic receptors which bind epinephrine, prostaglandin E_2 which bind prostaglandins.

Mechanism



A GPCR is made up of a long protein that has three basic regions: an extracellular portion (N-terminus), an intracellular portion (C-terminus) and the middle segment containing 7 trans-membrane domains.

→ When GPCR binds to a ligand (drug), the ligand triggers a conformational change in the 7 transmembrane region of the receptor.

→ This activates the C-termineus, which then activates the G-protein associated with GPCR.

→ Activation of G-protein initiates a series of intracellular reactions that produces a drug effect, such as heart rate in response to epinephrine.

2. Ion Channel Receptors

→ This is also called ligand gated ion channel receptors.

→ It is a large group of intrinsic transmembrane proteins that allow the passage of ions when activated by specific chemicals.

→ These are also surface receptors.

Mechanism

(Refer the diagram of ion channels in the section of mechanism of drug action)

→ An agonist bind with the ion channel by acting as an opener and opens up the channel.

→ Opening of channels allows the ions to move inside the cell in cytoplasm.

→ This changes the ionic composition of cell, resulting in depolarisation/ hyperpolarization.

→ Drug effect

Examples of ligand gated ion channels include cholinergic receptors, serotonin, $GABA_A$ and Glutamate receptor.

3. Transmembrane Enzyme-linked Receptor

As the name suggesting, these are the receptors which are associated to some enzymatic proteins.

→ When a drug binds to this type of receptor, it causes an enzyme to become "switched on" intercellularly.

→ This enzyme then catalyzes the formation of other signal proteins that ultimately lead to the cellular response.

→ The enzyme in most cases is a tyrosine proteins kinase.

→ Examples of receptors of this class are peptide hormones and cytokines.

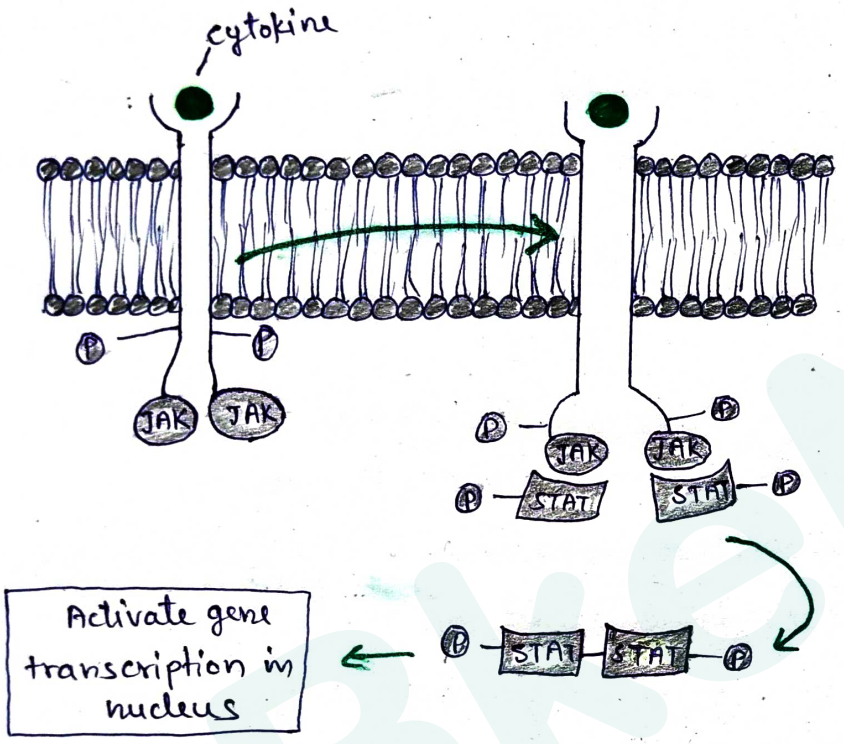
4. Transmembrane JAK-STAT binding receptor

JAK-STAT signalling is made of three major proteins:

1) cell surface receptors
2) Janus kinases (JAKs)
3) signal transducer and activation of transcription proteins (STATs).

JAK-STAT signalling pathway transmits information from chemical signals outside the cell, which causes DNA transcription and activity in the cell.

Mechanism



→ Cytokines bind to their receptors creating a dimerization of two separate cytokine subunits.

→ Dimerization activates the JAK proteins.

→ The kinase then phosphorylates parts of receptor subunits targeting tyrosines.

→ The phosphorylation attracts inactive STATS.

→ JAK kinases phosphorylates STATS which then dimerize.

→ The STATs can now receive nuclear signals and travel to the nucleus.

→ In the nucleus, STAT dimer activate transcription of different genes.

5. Receptors that regulate transcription factors

These receptors are intracellular soluble proteins which respond to lipid soluble chemical messangers that penetrate the cells,

These are the receptors that regulate gene expression

Nuclear Receptor

→ The lipid-soluble drugs diffuse through cell membrane and bind either in the cytosol or in the nucleus.

→ Gene expression is altered and protein synthesis is either increased or decreased, which causes cellular response.

→ Lipophilic substances such as steroid hormones and thyroid hormones acts through nuclear receptors.

Dose - Response Relationship

Dose → A dose is the amount of drug given to a patient at one time which produces a required effect in the body.

For example, if 500 mg of paracetamol is taken, then dose is 500 mg.

Response → It is the effect shown by the body to a particular drug.

For example, Paracetamol is antipyretic drug. So, it will bring the body temperature to normal as a response.

Dose-Response Relationship is used to analyze a kind of response obtained obtained after administering specific dose of drug.

For example, 10 mg of ILLAPRAZOLE inhibit the formation of proton pumps. It means it will inhibit the formation specifically at 10mg.

Dose-Response Relationship has two components:

(1) Dose - plasma concentration relationship

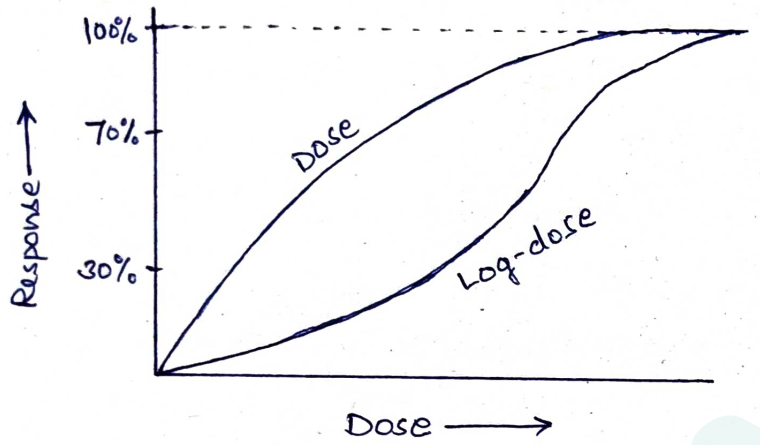
Higher the dose administered systemically, higher will be its concentration in blood plasma

(2) Plasma concentration - Response Relationship.

Higher the drug concentration in plasma, higher will be the response.

Dose-Response Curve

The graph plotted for a dose and its response is called dose-response curve.



→ Intensity of response increases with increase in dose and the dose-response curve is rectangular hyperbola.

This is because drug-response interaction obeys law of mass action:

$$E = \frac{E_{max} \times [D]}{K_d + [D]}$$

where,

E = observed effect of dose of drug

E_{max} = maximum response

K_d = dissociation constant

[D] = dose

Drug Potency → It is the amount of drug needed to produce a response.

But relative potency is more meaningful than absolute potency.

For example, if response of 10 mg of morphine = the response of 100 mg of pethidine.

It means morphine is 10 times more potent than pethidine.

Drug Efficacy → It refers to ability of drug to elicit a response when it binds with a receptor.

Therapeutic Index

Therapeutic index is the ratio of lethal dose and effective dose.

$$\text{Therapeutic Index} = \frac{LD_{50}}{ED_{50}}$$

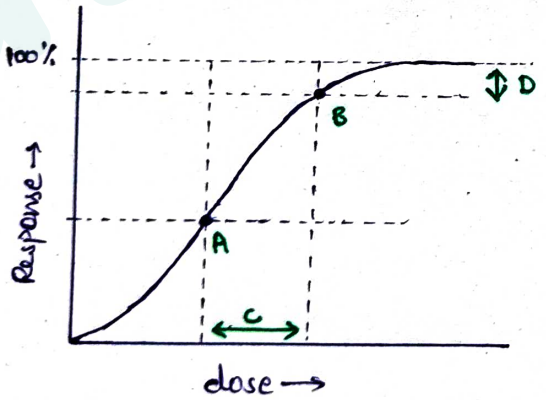
LD_{50} → it is that dose of a drug which will kill 50% of the individuals to which it is given.

ED_{50} → it is the dose which produces the deired effects and treats 50% of individuals.

Also, Minimum Effective Dose (MED) → which is the least dose that is able to produce the therapeutic effect.

On the other hand,

Maximum Tolerated dose (MTD) → This is the highest dose that will produce an effect. Above MTD, it can be toxic. So, it is also called minimum toxic dose.



Ⓐ → Minimum Effective Dose (MED)
Ⓑ → Maximum Tolerated Dose (MTD)
Ⓒ → Therapeutic Range
Ⓓ → Toxic dose

Therapeutic Range → It is the dose range b/w MED and MTD.

Toxic dose → It is the dose which will cause adverse effects.

Combined Effects of Drugs

Drugs given in combination of two or more drugs, they either increase the total effect or decrease it. Based on that, the combination may be synergism or antagonism.

1. Synergism

When the action of one drug is increased by the other in combination, they are said to be synergistic. Synergism is of further two types:

Additive → The effects of both the drugs add up and the total effect of both is equal to the sum of effects of individual drugs.

[Drugs(A+B) = Drug-A + Drug-B]

For example, the combination of paracetamol and aspirin provide effect of both, i.e., antipyretic + analgesic.

Supra-additive → The total effect is greater than the sum of effects of individual drugs.

[Effect of drug A+B > Drug-A + Drug-B]

For example, a combination of adrenaline and cocain that inhibit the neuronal uptake.

2. **Antagonism**

when one drug decreases the action of other, they are said to be antagonistic.

[Effects of drugs A+B < effect of drug-A + of drug-B

For example, Glucagon increases blood sugar level while insulin reduces it.

Factors Affecting Drug Action

(1) **Body size** → The normal dose is prepared for individuals of medium built. For exceptionally obese or lean individuals and for children, dose is calculated on the basis of body weight.

(2) **Sex** → Females have smaller body size and requires doses that are on the lower side of range.

(3) **Species and race** → Blacks require higher and mongols require lower concentrations of atropine and ephedrine to dilate their pupil.

(4) Route of Administration → A drug may have entirely different uses through different routes.

For example, magnesium sulfate given orally causes purgation, when applied on sprained joints decreases swelling, while given intravenously it produces CNS depression and hypotension.

(5) Environmental Factors → Exposure to insecticides, carcinogens, tobacco smoke are known to induce drug metabolism.

(6) Psychological factor → Efficacy of drug can be affected by patient's beliefs, attitude and expectations.

(7) Disease → Disease can influence drug action.

e.g. liver disease can alter metabolism of the drug and kidney disease can alter excretion of drug.

(8) Other drugs → Drugs can modify each other's response.

Adverse Drug Reactions

Adverse Drug Reactions (ADRs) are the undesirable effects of drugs on our body which occur at doses that are normal. ADRs may be trivial (not so serious), or may be fatal.

→ ADRs may occur immediately or after prolonged use after termination.

classification of ADRs

six types

1) Type-A (Augmented) Reactions
2) Type-B (Bizarre) Reactions
3) Type-C (Continuing) Reactions
4) Type-D (Delayed) Reactions
5) Type-E (End of use) Reactions
6) Type-F (Failure of Therapy) Reactions.

1) Type-A - Augment

→ dose-dependent (higher dose), preventable
→ predictable due to known pharmacology of drug.
→ mostly occur, less severe.
e.g. insulin induced hypoglycaemia, respiratory depression with opioids

(2) Type-B - Bizarre

→ usually hypersensitivity reactions (allergy)
→ not dose-dependent
→ non-predictable and usually not preventable
→ less common, more severe
e.g. penicillin induced allergy

3) Type-C → continuous

→ occurs after prolonged exposure to a drug.
→ dose and time dependant.
e.g. NSAID induced renal failure.

(4) Type-D → Delayed

→ they are seen after some time of drug use.
→ difficult to diagnose due to their timing.
e.g. thalidomide cause limb defects taken in first trimester.

(5) Type-E → End of use

Associated with withdrawal of a medicine.
e.g. Insomnia, anxiety after withdrawal of benzodiazepines.

6) Type-f → Failure of Treatment

Associated with failure of treatment due to causes such as inadequate information on the consumption, quality of drug, etc.
e.g. anti-tubercular therapy.

Causes of ADRs

- expired medicine
- overdosing, idiosyncracy
- Allergy to a particular medicine
- wrong medicine by mistake.

Prevention of ADRs

→ avoid inappropriate drugs
→ use right dose, route, frequency based on patient conditions.
→ History of allergy should be checked
→ Adopt right technique of medication and follow adequate monitoring during medication.

Drug Interactions

Drug interaction is defined as the change in pharmacological activity of one drug due to the presence of some other drug.

Drug interactions are:

(1) Mostly undesirable
(2) Rarely desirable (beneficial) e.g. enhancement of penicillin when administered with probenecid.

Factors contributing/causing drug interactions

1) Multiple prescribers and drug therapy
2) Multiple pharmacological effects of drug
3) Multiple diseases
4) Poor patient compliance
5) Drug-related factors.

Two types of interactions:

1) Pharmacokinetic interactions
2) Pharmacodynamic interactions.

Pharmacokinetic Interactions

These are those interactions in which ADME properties of the drug are altered by other drug.

These are classified as:

1. Absorption interactions
2. Distribution "
3. Metabolism "
4. Excretion "

1. Absorption Interactions → absorption of the drug is altered.
   → faster or slower drug absorption.
   → complete or incomplete absorption.

   Absorption interactions may be due to :
   1. complexation and absorption
   2. alteration in GI pH
   3. inhibition of GI enzymes
   4. alteration in GI micro flora (microorganisms)

   Example, Atropin and morphine together reduces absorption (slow gastric emptying)

2. Metabolism Interactions → metabolism of drug is altered.

   Metabolism interaction may be due to :
   1. Enzyme induction: increased metabolism rate
   2. Enzyme inhibition: decreased metabolism rate

   example, (corticosteroids + barbiturates)
   ↳ enzyme induction
   (Tyramine rich food + MAO inhibitors)
   ↳ Enzyme inhibition

3. Distribution Interactions → distribution pattern of drug is altered.
   → Distribution interactions may occur due to protein-drug binding alteration.
   e.g. Anti-coagulants and phenylbutazone increase clotting time.

4. Excretion Interactions → excretion pattern of drug is altered.
   e.g. Lithium bicarbonate NSAIDs causes decreased renal clearance of lithium.

   major causes of excretion interactions:
   1. alteration in renal blood flow
   2. alteration of urine pH
   3. competition for active secretions
   4. Forced diuresis

Pharmacodynamic Interactions

These are those interactions which alters the activity of drug at its site of action.
such interactions may be direct or indirect:

1. Direct Pharmacodynamic Interactions

Drugs have direct effects on each other's performance having similar or opposing pharmacological effects.
These may be:

- antagonism (opposing actions)
  e.g. Ach and noradrenaline have opposing effects on heart rate.
- Synergism (actions add up of both drugs)
  eg. Alcohol increases the analgesic activity of aspirin.

2. Indirect Pharmacodynamic Interactions

Drugs do not affect each other directly.
The effects of one drug may or may not be good for the action of another drug.
For example, salicylates decrease the ability of platelets to aggregate thus impairing the homeostasis if warfarin induced bleeding occurs.

Drug Discovery and Clinical Evaluation of New Drugs

Before any new drug becomes available in the market for treatment of specific disease, its harms and benifits are carefully studied.
Drug discovery is the process by which new candidate medications are discovered.
Drug development on the other hand is complete process of bringing this newly discovered drug to the market.

Aim:

- develop clinically efficacious and safer drugs
- economical viable drugs
- discover entirely new class of drugs
- explore the mechanism or pharmacodynamic properties of drugs.

Drug discovery and development process complites in following steps:

1) Target Selection
   a) Target Identification
   b) Target Validation
2. Lead Discovery
   a) Lead Identification
   b) Lead Optimization

Drug Discovery

3. Preclinical Trials/Studies
4. Clinical Trials/studies

Drug Development

1. Target Selection

Target selection in drug discovery means finding an agent having some therapeutic utility. This further has two steps:

a) Target identification → to identify molecular targets that are involved in a particular disease. But before that, the disease is identified, and reasons of it. Also, to find out which tissues or organs are involved in the disease.

b) Target Validation → this involves to prove or make sure that the choosen molecular target can provide therapeutic benfit for patients.

2. Lead Discovery

Lead compound is a chemical that has pharmacological activity likely to be therapeutically useful, but may still have structure that requires modification to fit better to the target.

a) Lead identification → find a compound that bind to target.

b) Lead optimization → Modify the lead compound to fit better to target.

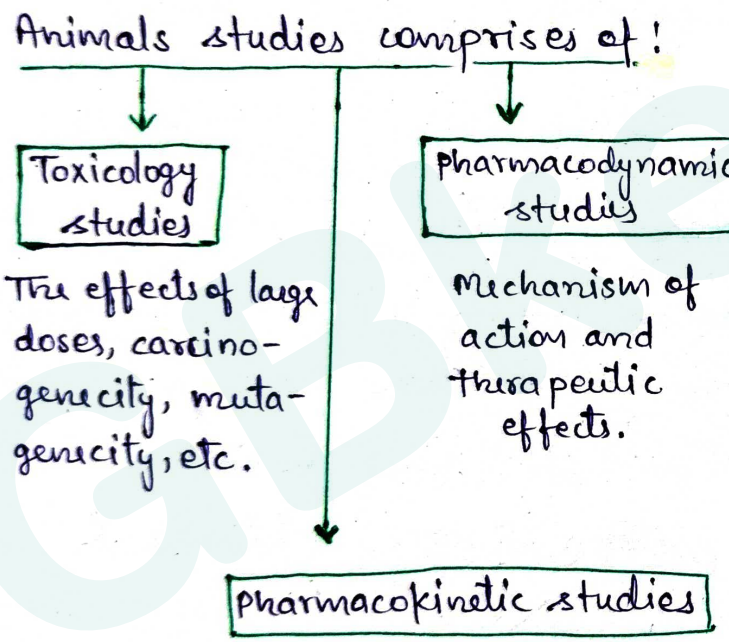
various modification types:

- functional group modification
- Structure - Activity Relationship (SAR)
- QSAR

3. Pre-clinical Phase

Before experimenting the newly discovered drug effects on humans, animals are used for this purpose. The experiment may be in-vitro or in-vivo.

Animals used for pre-clinical trials are mice, guinea pigs, rats, dogs, monkeys, cats, etc.



Objectives of Pre-clinical studies

→ to acquire enough data on animals to decide that it is safe to proceed trials on humans.

→ However, the main objective is to collect data to submit to the FDA for INDA filing.

INDA Filing

INDA → Investigational New Drug Application.

once preclinical studies have indicated the safety and efficacy of a drug, An IND application has to be filed with the regulatory authorities.

INDA has to be approved by regulatory bodies for the drug to enter clinical phase of trials.

Contents of IND application:

- Preclinical data
- Information on composition & source of drug
- chemical and manufactering information
- Proposed clinical plans and protocol
- Ethical commitee clearance

4. Clinical studies / Trials

During clinical studies, trials are conducted on humans.

Clinical trials are conducted in phases:

1) Phase-0
2) Phase-I
3) Phase-II
4) Phase-III
5) Phase-IV

1) Phase-0 / Microdosing → The aim of Phase-0 trials is not to test the therapeutic effects of drug but to check that the drug behaves as expected in humans.

A micro-dose is given, $1/100^{th}$ of the dose that is calculated to produce pharmacological effect.

objective: to obtain preliminary Pharmacokinetic (PK) data.

2) Phase-I Trials

→ The aim of a Phase-I trial is to determine maximum tolerated dose (MTD) of new treatment.
→ designed to assess the safety, tolerability, PK and Pharmacodynamic PD of drug.
→ 20-80 volunteers (duration 6-12 months)

3) Phase-II trials

→ Trial for therapeutic exploration.
→ consists of 100-500 patients
→ duration 6 months to several years.
→ objective: to confirm effectiveness, monitor side effects and further evaluate safety and to find dose range.

4) Phase-III trials

→ It is a therapeutic confirmation trial.
→ 1000-3000 patients
→ duration may be upto 5 years
→ To establish efficacy of the drug against existing therapy in larger number of patients.

→ To assess overall and relative therapeutic value of the new drug, efficacy, safety and special properties.

NDA: New Drug Application

It is the formal proposal for the FDA to approve a new drug for sale. Sufficient evidences provided to FDA for approval such as:

- drug is safe and effective
- benefits are more than risks.
- proposed labelling is done.

NDA contains all the information gathered during preclinical to phase-III.

4. Phase-IV trials → Post Marketing Surveillance (PMS).

→ No fixed number of patients and duration is also uncertain.

→ helps to detect rare ADRs, drug interactions and also to explore new uses of drugs

→ Harmful effects discovered may result in a drug being no longer sold or restricted to certain uses.

Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. All this done after the drug has been marketed. Pharmacovigilance basically refer to keep watching and monitoring that if the drug is not showing any side effects or any other problems in the large population.

Goals of pharmacovigilance

- early detection of unknown safety problems.
- detection of increase in frequency of ADRs
- identification of risk factors
- quantifying risks
- preventing patients from being affected unnecessarily.