PRINCIPLES OF PHARMACOLOGY

PHARMACOLOGY - is the study of drugs and their effects on life processes.

- **General pharmacology -** classification, characterization, evaluation, and comparison of all drugs
- **Pharmacokinetics -** Pharmacokinetics is concerned with the processes that determine the concentration of drugs in body fluids and tissues over time, including absorption, distribution, biotransformation, and excretion
- **Pharmacodynamics -** biochemical and physiological effects of drugs and their mechanisms of action)
- **Clinical pharmacology -** investigates new or established drugs in humans; is the basis for rational pharmacotherapy
- **Toxicology -** deals with the undesirable and harmful effects of chemicals on living systems

DRUG = MEDICATION

- any substance that brings about a change in biological function through its chemical actions
- natural product, chemical substance, or pharmaceutical preparation intended for administration to a human or animal to diagnose or treat a disease

A drug may be used:

- **substitutively** – Insulin
- **supportively** – oral hypoglycaemic agents
- **prophylactically** – Oral contraceptive tablets
- **symptomatically –**. Aspirin
- **diagnostically** – Histamine

MODE OF ACTION - the character of an effect produced by a drug.

MECHANISM OF ACTION - the molecular and biochemical events leading to an effect.

SITE OF ACTION - the receptor sites where a drug acts to initiate a group of functions.

CELLULAR SITES OF ACTION OF DRUGS

- because drugs are very reactive, they may elicit their effects/side effects by interacting with:
- coenzymes
- enzymes
- nucleic acids
- other macromolecules
- transport mechanisms

Inert binding sites

- components of endogenous molecules
- bind a drug
- no initiation events leading to any of the drug effect
- play important role in buffering the concentration of a drug

E.g.: two plasma proteins: albumin, α_1 – acid glucoprotein

Specific and nonspecific structure - activity relationships - an important aspect of pharmacology is to determine whether a drug effect is due to a **specific** structural component of the molecule or results from **nonspecific** drug action.

Specific drugs:

- interact with specific
- open or block ion channels
- modify transport systems
- inhibit or activate enzymes
- interfere with particular aspects of biosynthesis in microorganisms.

Specific drugs are usually **more potent** compared to nonspecific drugs. This means that:

- effects are seen with relatively lower drug concentrations
- activity is highly dependent on the chemical structure
- small structural changes can result in drastic changes in pharmacological activity
- drugs which act at the same site frequently have significant chemical similarities

Nonspecific drugs:

- do not specifically bind with a particular biological structure
- are active only in relatively high doses
- have similar activity but vastly different chemical structure
- show largely similar activity after chemical modification
- **Activity** of these nonspecific compounds is often related to lipophilicity (the activity differences among these compounds usually can be explained by differences in partition coefficients)
- These drugs interact with lipophilic cell components to alter cellular membrane function.

Natural sources of drugs

- **plants** – alkaloids (morphine, atropine)
- **microbes** – antibiotics (penicillin)
- **animal tissues** – hormones (insulin)
- **minerals** (lithium)

Pharmaceutical preparations <u>compounded individually:</u>

- prepared individually for a particular patient according to the physician's prescription in a pharmacy licensed for compounding
- **<u>individualization</u>** the pharmacotherapy when:
- the drug in a particular dosage form is not commercially available
- the extraordinary low or high dose is needed (children, elderly people, special situations)
- patient is unable to use drug in its commercially available dosage form
- allergy on a specific excipients
- **<u>lack of standardization</u>**

<u>Manufactured</u> pharmaceutical preparations:
Original pharmaceutical preparations:

- full and very extensive pharmacological/toxicological and pharmaceutical pre-clinical and clinical evaluation
- the proof of effectiveness and safety

Generic pharmaceutical preparations (authorised copies of original preparations):

- can be released after the expiration of the patent protection of the original preparation
- easier approval for clinical use due to the prior experience with the original preparation

Original vs. Generic preparations:
<u>Must be pharmaceutically equivalent</u>:

- same active ingredient
- dose
- route of administration

<u>Must be clinically bioequivalent:</u>

- similar PK profile
- PK parameters (Cmax, tmax, AUC) are within 80-125 % range as compared with the original preparation

<u>Don't have to be therapeutically equivalent:</u>

- comparing directly the clinical effectiveness is not commonly required

<u>PHARMACODYNAMICS -</u> the study of detailed **mechanism of action** by which drugs produce their pharmacologic effects.
(**„How drugs work on the body").**

The main ways by which drugs act are via interaction with **<u>cell proteins:</u>**

- receptors
- ion channels
- enzymes
- transport/carrier proteins

DRUG RECEPTOR:

- a macromolecular component of a cell with which a drug interacts to produce a response
- usually a **protein**
- receptors are found **in the cell membrane**, **in the cytoplasm**, and **in the nucleus**
- drugs often work by binding to a "receptor"
- anything that binds to a receptor is a **"ligand"**

ROLE OF DRUG RECEPTORS:

- determine the quantitative relations between **dose or concentration** of drug and pharmacologic **effects**
- are responsible for **selectivity** of drug action
- mediate the actions of pharmacologic antagonists

<u>TYPES OF RECEPTORS:</u>

1) LIGAND GATED ION CHANNEL (IONTROPIC RECEPTORS):

- signal molecule binds as a ligand at a specific site on the receptor
- conformational changes open the channel allowing ions to flow into the cell
- the change in ion concentration within the cell triggers cellular response

2) G PROTEIN COUPLED RECEPTORS:

- Drug binds to a G protein-linked receptor
- Receptor changes shape and interacts with G protein
- GDP is displaced and GTP is bound to G protein
- Active G protein binds another protein (e.g., enzyme)
- The enzyme is activated
- G protein hydrothyzes GTP back to GDP
- G protein releases from the enzyme; the reaction stops

3) KINASE LINKED RECEPTORS:

- Ligands bind to both receptors
- The two receptor polypeptides aggregate forming a dimer
- Activates the tyrosine kinase parts of the dimer
- Each phosphorylates (using ATP) the tyrosine on the

tail of the other polypeptide
- Receptor proteins are recognized by relay proteins inside the cell
- Relay proteins bind to the phosphorylated tyrosines (may activate 10 or more different transduction pathways)

4) INTRACELLULAR RECEPTORS:

- proteins located in the cytoplasm or nucleus of target cells
- the signal molecule must be able to pass through plasma membrane

SECOND MESSENGERS:
- small, nonprotein, water-soluble molecules or ions
- readily spread throughout the cell by diffusion

Most widely used second messengers are:
- Cyclic Adenosine Monophosphate (cAMP)
- Calcium ions Ca^{2+} and Phosphoinositides
- Cyclic Guanosine Monophosphate (cGMP)

RELATION BETWEEN DRUG DOSE & CLINICAL RESPONSE (DOSE RESPONSE CURVES):

Arithmetic Dose Scale
- there is an increase in response with increasing dose of a drug until it reaches maximum
- rate of change is rapid at first and becomes progressively smaller as the dose is increased
- maximal effect for that drug is obtained
- increments in dose produce no further change in effect – *Plateau effect*
- difficult to analyse mathematically

Log Dose Scale
- transforms hyperbolic curve to a sigmoid (almost a straight line)
- compresses dose scale
- proportionate doses occur at equal intervals
- straightens line, easier to analyse mathematically

DRUG-RECEPTOR INTERACTION:
- a **drug** (D) binds to a **receptor** (R) in a reversible reaction
- **D + R ↔ DR ↔ DR* →→→→ Response**
- this conformational change leads to a series of events causing a **cellular response**

SPARE RECEPTORS:
- receptors are said to be ***SPARE*** when maximal response can be elicited by an agonist at a conc. that does not result in occupancy of the full complement of available receptors
- **no qualitative difference** form non spare receptors

Drugs are described based on the magnitude of its properties:

AFFINITY for the receptor – affinity is related to potency

EFFICACY
- once bound to the receptor – efficacy refers to the maximal effect the drug can elicit
- maximum effect of the drug
- height of the curve on x-axis indicates the efficacy of the drug
- taller the DRC ,more efficacious the drug

POTENCY
- is a measure of how much drug is required to elicit a given response
- the lower the dose required to elicit given response, the more potent the drug is
- dose of a drug that required to produce 50% of maximal effect (**ED_{50}**)
- relative positions of the DRC on x-axis
- more left the DRC, more potent the drug

ED_{50}
- it is the dose of the drug at which it gives 50% of the maximal response
- a drug with low ED_{50} is more potent than a drug with larger ED_{50}

SLOPE OF DRUG RESPONSE CURVE (DRC)

STEEP DRC
- moderate increase in dose leads to **more** increase in response
- dose **needs** individualization for different patients
- unwanted and uncommon

FLAT DRC
- moderate increase in dose leads to **little** increase in response
- dose ***needs no*** individualization for different patients
- desired and common

DRUG-RECEPTOR INTERACTION:

When a drug binds to a receptor the following can occur and based on this the drugs are classified:
- **antagonists** can bind to the receptor and occupy its binding site and, therefore, participate only in the first equilibrium
- **agonists** have the appropriate structural features to force the bound receptor into an active conformation (DR*)

AGONIST (Full agonist):
- a drug that binds to the receptor and activates it to produce an effect
- *has affinity for receptor and efficacy*
- e.g., ACh is agonist at muscarinic receptor in heart cell

PARTIAL AGONIST:

- a drug that binds to the receptor and activates it but produces a submaximal effect (by antagonising the full effect of the agonist)
- *has affinity but lower efficacy than full agonist*

INVERSE AGONIST:

- a drug that activates a receptor to produce an effect in the opposite direction to that of the agonist
- *have* ***affinity*** *and negative* ***intrinsic activity***
- E.g., Flumazenil is an inverse agonist of Benzodiazepine

ANTAGONIST:

- a drug that binds to a receptor and prevents the action of an agonist
- does not have an action on its own
- *has affinity but no efficacy*
- E.g., Atropine is antagonist of ACh at Muscarinic receptors

COMPETITIVE ANTAGONIST:

- competes with agonist for receptor
- surmountable with increasing agonist concentration
- displaces agonist dose response curve to the right (dextral shift)
- reduces the apparent affinity of the agonist

NONCOMPETITIVE ANTAGONIST:

- produces slight dextral shift in the agonist DR curve in the low concentration range
- this looks like competitive ANT
- but, as more and more receptors are bound, the AG drug becomes incapable of eliciting a maximal effect

COMBINED EFFECT OF DRUGS:

When two drugs are given together or in quick succession 3 things can happen:

- Nothing (indifferent to each other)
- Action of one drug is facilitated by the other **(SYNERGISM)**
- Action of one drug may decrease or inhibit the action of other drug **(ANTAGONISM)**

SYNERGISM:

Additive effect: the effect of two drugs are in the same direction and simply add up

Effect of drug A + B = effect of drug A and B

Supraadditive effect (potentiation): the effect of combination is greater than the individual effect of the components.

Effect of drug A+B > effect of drug A+effect of drug B

ANTAGONISM:

Physical: based on physical property of a drug

e.g. activated charcoal adsorbs alkaloids and prevents their absorption (in alkaloid poisoning)

Chemical: based on chemical properties resulting in an inactive product

e.g. chelating agents complex metals (used in heavy metal poisoning)

Physiological: based on physical property of a drug

e.g. activated charcoal adsorbs alkaloids and prevents their absorption (in alkaloid poisoning)

Receptor antagonism: based on chemical properties resulting in an inactive product

e.g. chelating agents complex metals (used in heavy metal poisoning)

Receptor antagonism:

- an antagonist interferes with the binding of the agonist with its receptor and inhibits the generation of a response
- receptor antagonism is **specific**
- e.g. an anticholinergic will decrease the spasm of intestine induced by cholinergic agonists but not the one induced by histamine
- receptor antagonism can be **competitive** and **noncompetitive**

COMPETITIVE antagonism:

- antagonist binds with same receptor
- chemical resemblance with agonist
- parallel rightward shift of DRC
- apparently reduces potency of agonist
- intensity of response depends both on antagonist and agonist concentration
- eg: Acetylcholine and Atropine

NONCOMPETITIVE antagonism:

- another site of receptor binding
- does not resemble
- flattening of DRC
- apparently reduces efficacy of agonist
- intensity of response depends mainly on antagonist concentration
- eg: phenoxybenzamine (for pheochromocytoma)

QUANTAL DOSE RESPONSE CURVES:

- Quantal dose-effect curves are used to generate information regarding the margin of safety (Therapeutic index)

ED50 – *Median Effective Dose 50* – the dose at which 50 percent of the population or sample manifests a given effect.
TD50 – *Median Toxic Dose 50* – the dose at which 50 percent of the population manifests a given toxic effect.
LD50 – *Median Lethal Dose 50* – the dose which kills 50 percent of the subjects

THE THERAPEUTIC INDEX:

- the higher the **TI** the better the drug
- vary from 1.0 (some cancer drugs) to >1000 (penicillin)
- drugs acting on the same receptor or enzyme system often have the *same* **TI** (eg 50mg of hydrochlorothiazide about the same as 2.5mg of indapamide)

Clinical significance:

- Drugs with a low TI should be used with caution and needs a periodic monitoring (less safe)
- E.g. warfarin, digoxin, theophylline
- Drugs with a large TI can be used relatively safely and does not need close monitoring (highly safe)
- E.g. penicillin, paracetamol

REGULATION OF RECEPTOR NUMBERS AND RESPONSE:

Sensitization or Up-regulation of receptors:

- an increase in receptor number on the surface of target cells, making the cells more sensitive to a hormone or another agent
- prolonged/continuous use of receptor blocker
- e.g., there is an increase in uterine oxytocin receptors in the third trimester of pregnancy, promoting the contraction of the smooth muscle of the uterus
- inhibition of synthesis or release of hormone/neurotransmitter - Denervation

Desensitization or Down-regulation:

- a decrease in receptor number
- prolonged/continuous use of agonist
- inhibition of degradation or uptake of agonist
- e.g., prolonged use of propranolol can DECREASE the number of β_1 receptors
- e.g., Prolonged & frequent use of short acting β_2 receptor agonists decrease the number of β_2 receptors
- clinical relevance: a patient's response to drug therapy may change over time

PHARMACEUTICAL DOSAGE FORMS

Classification according to the physical properties:

Gaseous dosage forms:

- **Sprays** - are composed of various bases such as alcohol or water in a pump-type dispense
- **Inhalants and Aerosols –** variety of forms – all must be easily inhaled into the lungs; devices – nebulizers and humidifiers

Liquid dosage forms:

- **Solutions** – can be administered by all routes
- **Syrups –** sugar-based aqueous solutions that have medications dissolved in them

Good option for young children!

- **Drops (eye, ear, nasal)** – eye drops – must be sterile
- **Elixirs** – sweetened solutions containing dissolved medication in an alcohol base
- **Tinctures** –alcoholic herbal extract
- **Emulsion –** a dispersion system consisting of two immiscible liquids used with an emulsifier binds the two together
- **Suspension –** a dispersion system where solid particles are dispersed in liquid phase

Not intended for systemic administration of drugs with high potency !

- **Injections** (available as ampoules, vials with rubber head) – solutions, emulsions or suspensions
- **Infusions** (available in plastic bags) – higher volumes over much larger times (from min to days)

Sterile, pyrogen-free, isotonic!

Semisolid dosage forms:

- **Ointments, Gels, Creams**

Solid dosage forms:

Unshaped

- **Powders** for external/internal use

Shaped

- **Tablets**
  - Effervescent tablets (the final dosage form is a solution)
  - Sublingual tablets (under the tongue)
  - Buccal tablets (between the gum and cheek)
  - Chewable tablets (if swallowing difficulty and for children)
- **Capsules –** soft and hard
- **Transdermal patches** – transdermal patches designed for affixing on the skin; controlled drug delivery into the systemic circulation over time
- **Suppositories (**rectal, urethral, vaginal)

ROUTES OF ADMINISTRATION

Oral Route (P.O.)

- **by mouth; systemic or local effect**
- very convenient, the most common, the easiest, safe
- do not need to be measured
- most economical
- do not work as quickly as parenterally (IV's)
- some drugs cannot be taken orally because they are not as effective
- unpleasant taste, gastric upset, constipation, diarrhea, teeth stain
- drugs administrated with sufficient amount of water
- correct time of administration
- with food or on an empty stomach

Sublingual and Buccal Route:

- **buccal** agents are placed between the gum and cheek
- **sublingual** agents are placed under the tongue
- the medication penetrates the mouth lining and then enters the bloodstream – **systemic effect**
- tablets, spray
- *Example: nitroglycerin - in anginal attacks*

Vaginal Route:

- **for local drug administration – only local effect**
- **Tablets**, c**apsules, globules** – disintegrating in vagina; may also form foam
- **Foams, Creams -** application devices
- *Example: antimicrobial agents*

Rectal Route:

- rectal dosage forms (suppositories, gels, creams, enemas) for **local and systemic** drug administration
- it can bypass the liver - there may be no first pass effect
- when patient cannot swallow the drug (unconsciousness, vomiting, serious GIT disturbances)
- useful for children
- uncomfortable (poor compliance)
- actual amount of drug absorbed is hard to predict
- local irritation of rectal mucosa
- low stability during at high temp.

Topical Route:

- effects range from **localized** (at the site of action) to **systemic** (absorbed into the blood stream)
- easy application
- **dosing is difficult**
- Gaseous dosage forms – sprays
- Liquid dosage forms – lotions, shampoo, foam
- Semisolid dosage forms – gels, creams, ointments
- Solid dosage forms – dusting powder
- *Example: antimicrobial*

Transdermal Route:

- **Transdermal drug delivery systems (TDDS)**
- pain- and stress-free
- easily administered – no need for trained specialist
- long-term drug delivery with minimal fluctuations of drug concentrations
- good compliance
- delivery of the drug can be immediately discontinued
- eliminate a possible upset stomach
- not feasible for all API
- local reactions/irritation
- *Examples: hormones, opioid analgesics, nitroglycerine, nicotine*

Parenteral Route:

- parenteral comes from the Greek and means "side of intestine" or "outside of intestine"
- for medications entering the body through any route **other than orally** through the gastrointestinal system
- **Intravenous (IV), Intramuscular (IM), Subcutaneous (SC)**

It can be a approach of choice in the case of:

- problems with oral absorption (poor/erratic)
- problems with stability of API in GIT (pH, enzymes)
- uncooperative patients (unconsciousness, vomiting)
- urgent need for rapid onset of action (emergencies)

Limited use due to:

- non-compliance (phobias, children)
- higher risk of adverse reactions (pain/irritation at the site of injection)
- accidental extravasation of some drugs – tissue inflammation, necrosis
- need for trained personnel using aseptic procedures
- more expensive
- once a drug is injected, there is little time to alter its course

Local drug administration <u>into the eye:</u>

- high local concentration
- lower systemic adverse reactions
- minor effects on vision – liquid dosage forms (drops)
- API exposure is longer – semisolid dosage forms (gels, ointments) - can hinder vision
- slow release of API – eye inserts
- if not kept sterile during use, can introduce bacteria into the area being treated
- do not last as long as other treatments – blinking of the eye and tearing
- dosage accuracy
- local hypersensitivity
- *for infections, inflammation, and glaucoma*

THE PRESCRIPTION

- is a written order for medication to be used for the diagnosis, prevention, or treatment of a specific patient's disease by a licensed physician, dentist, or veterinarian

THE PRESCRIPTION CONSISTS OF:

Part of the prescription	Information
the superscription	• date • patient's data: name, address, weight, age • symbol of the prescription „Rx"
the inscription	• the name, amount, strength (dose) of the drug
the subscription	• the instruction to the pharmacist, how to prepare or dispense the drug
the signa (the transcription)	• the instruction for the patient, how to take the prescribed drug
the data of the prescriber	• the name and signature of the prescriber • the address, the phone number • the professional degree and registration number of the prescriber

CLASSES OF PRESCRIPTION ORDERS

- **Precompounded prescription order** – calls for a drug or mixture of drugs supplied by the pharmaceutical company by its official or proprietary name and in a form that the pharmacist dispenses without pharmaceutical alteration.
- **Extemporaneous prescription order (also called compounded)** – is the type in which the physician selects the drugs, doses, and pharmaceutical form that he desires and the pharmacist prepares the medication.

THE ORDER OF INGREDIENTS

- Basis – a principal drug, that gives the prescription its chief action
- Adjuvant – a drug that aids or increases the action of the principal ingredient
- Corrective – a substance which modifies or corrects undesirable effects of the basis or adjuvant
- Vehicle – an agent used as the solvent in the solution, to increase the bulk, or to dilute the mixture

The prescription writing – general rules:

- poor handwriting is a well-known and preventable cause of dispensing errors
- all orders should be written using metric measurements of weight and volume
- Arabic numerals are preferable to Roman numerals
- use leading zeros (0.125 mg, not .125 mg)
- don't use trailing zeros (5 mg, not 5.0 mg)
- avoid abbreviating drug names (*For example: an order for administration of magnesium sulphate must not be abbreviated „MS", as this may result in administration of morphine sulphate)*
- avoid abbreviating directions for drug administration

COMPLIANCE

- may be defined as the extent to which the patient follows a regimen prescribed by a healthcare professional
- the patient is the final and important determinant of how successful a therapeutic regimen will be
- collaborative interaction between physician and patient in which each brings an expertise that helps to determine the course of therapy
- the physician - the medical expert
- the patient - the expert on himself, his beliefs, values, and lifestyle

Suggestions for improving Patient Compliance provide respectful communication:

- ask patients how they take medicine
- develop satisfactory, collaborative relationship between physician and patient
- encourage pharmacist involvement
- provide and encourage use of medication counselling
- give precise, clear instructions, with most important information given first
- support oral instructions with easy-to-read written information
- simplify whenever possible
- assess patient's literacy and comprehension and modify educational counselling as needed
- don't rely on patient knowledge about his or her disease
- use mechanical compliance aids as needed (sectioned pill boxes, compliance packaging, color-coding)
- use optimal dosage form and schedule for the individual patient
- find solutions when physical or sensory disabilities are present (use non-safety caps on bottles, use large type on labels and written material, place tape marks on syringes)
- enlist support and assistance from family or caregivers
- use behavioural techniques such as:
- goal setting
- self-monitoring
- cognitive restructuring
- skills training
- contracts
- positive reinforcement

Consequences of noncompliance:

- lack of the intended therapeutic benefits
- recurrence or worsening of the illness
- emergence of antibiotic-resistant microorganisms
- prescribing of a larger dose or a more potent agent that could lead to toxicity if compliance is improved