Odesa National Medical University
Department of General and Clinical Pharmacology
and Pharmacognosy

GENERAL PHARMACOLOGY

Basic definitions

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes. The interactions between a drug and the body are conveniently divided into two classes.

The actions of the drug on the body are termed **pharmacodynamic processes.**

The actions of the body on the drug are called **pharmacokinetic processes**. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs.

Pharmatoxicodynamics is that branch of pharmacology that deals with the undesirable effects of chemicals on living systems.

PHARMACOKINETICS

Principles of drug transfer.

- **Passive or lipid diffusion** due to gradient of substance's concentration.
- **Filtration or aqueous diffusion** is appear across epithelial membrane through pores that permit the passage of small molecules.
- **Active transport** is provided by special carrier molecules exist.
- **Pinocytosis** is the process by which the substance is engulfed by the cell membrane and carried into the cell by pinching off of the newly formed vesicle inside the membrane.

ROUTES OF DRUGS' ADMINISTRATION

- **Enteral route** include **oral, subglossal,** and **per rectum** administration.
- **Parenteral route** include **injections, inhalations,** and **transdermal** route.

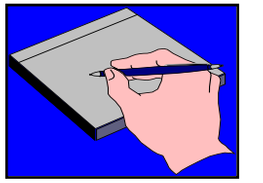
Bioavailability is the ratio of unchanged drug reaching the systemic circulation to the given dose (in percentage).

For a drug administered orally, bioavailability may be less than 100% for two main reasons - incomplete extent of absorption and *first-pass elimination*. The last one is mean that following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation.

DISTRIBUTION OF THE DRUGS

There are three fractions of substances in organism:

- **free fraction in serum and tissues**;
- **connected with serum proteins**;
- **fixed in different tissues**.



Initially, liver, kidney, brain and other well-perfused organs receive most of the drug, whereas delivery to muscle, most viscera, skin, and fat is slower.

Volume of distribution (Vd) relates the amount of drug in the body to the concentration of drug (C) in blood or plasma:

Vd = Amount of drug in body / C

BIOTRANSFORMATION

In general, biotransformation reactions generate more polar, inactive metabolites that are readily excreted from the body.

- ✓ **Phase I reactions** (functionalization or metabolism) **usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2).**
- ✓ **Phase II reactions** (conjugation or biosynthetic) **in which an endogenous substrate such as glucuronic acid, sulfuric acid, or acetic acid combines with the newly established functional group**

Factors affecting drug metabolism.

1. **Genetic variation.**
2. **Environmental deteminants (enzyme induction or inhibition).**
3. **Diseases, age, sex.**

EXCRETION OF THE DRUGS

Drugs are eliminated from the body either inchanged by the process of excretion or coverted to metabolites.

Renal excretion. The amount of drug entering the tubular lumen by filtration is dependent on the glomerular filtration rate and the extent of plasma binding of the drug. In the proximal renal tubule, active, carrier-mediated tubular secretion also may add drug to the tubular fluid.

Biliary and fecal excretion.

Elimination is the process of drug inactivation in result of biotransformation and excretion.

Half-life **(T*1/2*)** is the time required to change the amount of drug in the body (usually in blood) by one-half during elimination time.

Total clearance of a drug is the ratio of the rate of elimination by all routes to the concentration of drug in serum.

PHARMACODYNAMIC PROCESSES

Most drugs act by associating with specific macromolecules in ways that alter the macromolecules' biochemical or biophysical activities. This idea is embodied in the terms **receptive substance** and **receptor:** the component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects.

Agonists (mimetics) bind to physiological receptors and mimic the regulatory effects of the endogenous signaling compounds.

Antagonists (lytics, blockers) bind to receptors without regulatory effect, but their binding blocks the binding of endogenous agonist.

Macromolecular nature of drug receptors

- ✓ regulatory proteins, like neurotransmitters, autacoids, and hormones
- ✓ enzymes (eg, dihydrofolate reductase, the receptor for the antineoplastic drug methotrexate)
- ✓ transport proteins (eg, Na□/K□ ATPase, the membrane receptor for cardioactive digitalis glycosides) ,
- ✓ structural proteins(eg, tubulin, the receptor for colchicine, an anti-inflammatory agent).

SIGNALING MECHANISMS & DRUG ACTION

- **Intracellular receptors for lipid-soluble agents.**

  Several biologic signals are sufficiently lipid-soluble to cross the plasma membrane and act on intracellular receptors through which they stimulate the transcription of genes.

- **Ligand-regulated transmembrane enzymes.**

  These receptors are polypeptides consisting of an extracellular hormone-binding domain and a cytoplasmic enzyme domain, which may be a protein tyrosine kinase, etc

SIGNALING MECHANISMS & DRUG ACTION

- **Ligand-gated channels.**

  These channels regulate the flow of ions through plasma membrane channels, e.g., nicotinic-cholinoreceptors

- **G proteins & second messengers,** like

  cAMP (beta-adrenomimetics);

  diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP3) (M-cholinergic agents);

  cGMP.

RELATION BETWEEN DRUG CONCENTRATION AND RESPONSE

A. Graded dose-response relations.

To choose among drugs and to determine appropriate doses of a drug, the prescriber must know the relative **pharmacologic potency** and **maximal efficacy** of the drugs in relation to the desired therapeutic effect.

Potency refers to the concentration (EC50) or dose (ED50) of a drug required to produce 50% of that drug's maximal effect.

The **maximal efficacy** is the maximal possible effect of the drug.

RELATION BETWEEN DRUG CONCENTRATION AND RESPONSE

B. Quantal dose-effect curves.

Median effective dose (ED50), the dose at which 50% of individuals exhibit the specified quantal effect.

Median toxic dose (TD50), the dose required to produce a particular toxic effect in 50% of animals. If the toxic effect is death of the animal, a **median lethal dose (LD50)** may be experimentally defined.

Therapeutic index relates the dose of a drug required to produce a desired effect to that which produces an undesired effect (TD50 to the ED50).

TYPES OF DRUG'S ACTION.

- ✓ **Local action** is the drug's action in place of administration
- ✓ **Resorptive action** is observed after drug achievement of blood.

- ❑ **Direct action** occurs in the place of drug contact with tissues,
- ❑ **Indirect action** appears in result function changes

- **Basic action** is the main goal of drug's administration
- **Side action** is an additional effect to basic action.

- ➢ **Selective action** alters function of certain organ and system.
- ➢ **General action** is non-specific action in different organs and tissues

TYPES OF DRUG'S ACTION.

- **Convertible (reversible)** action disappears just after drug's elimination.
- **Non-convertible (irreversible)** action appears in result of strong connection of drug with receptor (usually covalent) that cause irreversible breaking off it function.

- **Selective action** alters function of certain organ and system.
- **General action** is non-specific action in different organs and tissues

FACTORS THAT INFLUENCE ON DRUG'S ACTION

Features of drugs

structure of drug, it's physical and chemical features, pharmaceutical form, and doze.

Factors related with whole organism

age, sex, genetic features, condition of patient, and biological rhythms.

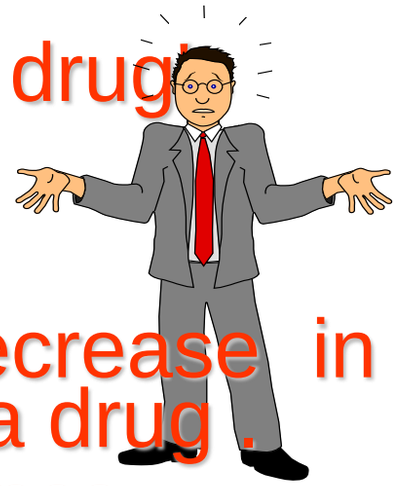
Environmental factors

stress, strong noises, vibration, radiation, ecological problems,

CHANGES IN DRUG'S ACTION WHILE REPEATED ADMINISTRATION

Cumulation

- ***Material cumulation*** is the accumulation of drugs (e.g., digitoxine, strychnine) that are slowly excreted from organism.
- ***Functional cumulation*** is the accumulation of drug's effect (alcohol, caffeine, etc.).



Tolerance

- ***Tolerance*** is appearance of progressive decrease in response following repetitive administration of a drug .
- ***Tachyphylaxis*** is a rapid appearance of tolerance

Dependence

- **Dependence** is characterized by constant and repeated wish of drug using. Usually it is indicated by **withdrawal symptoms (abstinence)** that develop when use of the substance is terminated. .

CHANGES IN DRUG'S ACTION WHILE REPEATED ADMINISTRATION

Dependence

- **Psychologic dependence** is manifested by compulsive drug-seeking behavior in which the individual uses the drug repetitively for personal satisfaction.
- **Physiologic dependence** is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user.

DRUGS INTERACTIONS

Pharmaceutical

may appear between incompatible drugs while their production, storing or mixing in solution

Pharmacokinetic

can be observed during absorption, transport, biotransformation, and excretion of drugs

Pharmacodynamic

appears in form of synergism or antagonism