PHARMACOLOGY

is the **study of substances** that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

TOXICOLOGY

A branch of pharmacology which deals with the **undesirable effects** of chemicals on living systems, from individual cells to complex ecosystems.

MEDICAL PHARMACOLOGY

Is defined as the science of substances used to **prevent, diagnose, and treat disease.**

Reasons for different Routes of Administration:

• For convenience – oral drugs
• To maximize concentration at the site of action and minimize it elsewhere (topical)
• To prolong the duration of drug absorption (transdermal)
• To avoid the first pass effect

Weak Acid and Weak Base

Weak acid - is a neutral molecule that can reversibly dissociate into an anion and a proton

Weak base - a neutral molecule that can form a cation by combining with a proton.

Application of the principle:
- **Acidic drugs** are best absorbed from acidic environments
- **Basic drugs** are best absorbed from basic environments

Thus, **weak acids** are usually excreted faster in alkaline urine; **weak bases** are usually excreted faster in acidic urine.

Table 1 - 4

TABLE 1–3 Ionization constants of some common drugs.

Drug	pK_a	Drug	pK_a	Drug	pK_a
Weak acids		**Weak bases**		**Weak bases (cont'd)**	
Acetaminophen	9.5	Albuterol (salbutamol)	9.3	Isoproterenol	8.6
Acetazolamide	7.2	Allopurinol	9.4, 12.3[2]	Lidocaine	7.9
Ampicillin	2.5	Alprenolol	9.6	Metaraminol	8.6
Aspirin	3.5	Amiloride	8.7	Methadone	8.4
Chlorothiazide	6.8, 9.4[2]	Amiodarone	6.6	Methamphetamine	10.0
Chlorpropamide	5.0	Amphetamine	9.8	Methyldopa	10.6
Ciprofloxacin	6.1, 8.7[2]	Atropine	9.7	Metoprolol	9.8
Cromolyn	2.0	Bupivacaine	8.1	Morphine	7.9
Ethacrynic acid	2.5	Chlordiazepoxide	4.6	Nicotine	7.9, 3.1[2]
Furosemide	3.9	Chloroquine	10.8, 8.4	Norepinephrine	8.6
Ibuprofen	4.4, 5.2[2]	Chlorpheniramine	9.2	Pentazocine	7.9
Levodopa	2.3	Chlorpromazine	9.3	Phenylephrine	9.8
Methotrexate	4.8	Clonidine	8.3	Physostigmine	7.9, 1.8[2]
Methyldopa	2.2, 9.2[2]	Cocaine	8.5	Pilocarpine	6.9, 1.4[2]
Penicillamine	1.8	Codeine	8.2	Pindolol	8.6
Pentobarbital	8.1	Cyclizine	8.2	Procainamide	9.2
Phenobarbital	7.4	Desipramine	10.2	Procaine	9.0
Phenytoin	8.3	Diazepam	3.0	Promethazine	9.1
Propylthiouracil	8.3	Diphenhydramine	8.8	Propranolol	9.4
Salicylic acid	3.0	Diphenoxylate	7.1	Pseudoephedrine	9.8
Sulfadiazine	6.5	Ephedrine	9.6	Pyrimethamine	7.0–7.3[3]
Sulfapyridine	8.4	Epinephrine	8.7	Quinidine	8.5, 4.4[2]
Theophylline	8.8	Ergotamine	6.3	Scopolamine	8.1
Tolbutamide	5.3	Fluphenazine	8.0, 3.9[2]	Strychnine	8.0, 2.3[2]
Warfarin	5.0	Hydralazine	7.1	Terbutaline	10.1
		Imipramine	9.5	Thioridazine	9.5

PHARMACOKINETICS

The goal of therapeutics is to achieve a desired beneficial effect with **minimal adverse effects.**

the actions of the **body on the drug.**

determine how rapidly and for how long the drug will appear at the target organ.

Pharmacokinetics deals with the dose-concentration part.

this govern the **Absorption, Distribution, and Elimination** of drugs

PHARMACOKINETIC PRINCIPLES

PRODRUG - an inactive precursor chemical that is readily absorbed and distributed is administered and then converted to the active drug by biologic processes – inside the body.

FREE DRUG - exerts a biologic effect

BOUND DRUG - stays in the vascular space and is not metabolized or eliminated.

PHARMACOKINETIC PRINCIPLES (cont)

PERMEATION - is the **movement of drug molecules** into and within the biologic environment.

The NATURE of DRUGS:

Drug - any substance that **brings about a change** in biologic function through its chemical actions.

the drug molecule interacts as an **agonist** (activator) or **antagonist** (inhibitor) with a specific target molecule that plays a regulatory role in the biologic system.

Drugs maybe synthesized within the body (eg. **Hormones**) or maybe chemicals not synthesized in the body, ie. **Xenobiotics** (xenos – "stranger")

Poisons - are drugs that have almost exclusively harmful effects. (**Paracelsus** – famously stated "the dose makes the poison" --- any substance can be harmful if taken in the wrong dosage)

Toxins - are defined as **poisons of biologic origin**, synthesized by plants or animals

ROLE OF BIOTRANSFORMATION IN DRUG DISPOSITION

Phase 1 Reactions	usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (–OH, –NH2, –SH).

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ROLE OF BIOTRANSFORMATION IN DRUG DISPOSITION (cont)

	• If phase I metabolites are sufficiently polar, they may be readily excreted.
	- involves **oxidation, reduction, hydrolysis**
	- alter chemical reactivity and increase aqueous solubility
PHASE II reactions	- involves **conjugation**
	this reaction further increases the solubility, promoting elimination

Plasma Protein Binding:

if a drug is displaced from plasma proteins it would increase the unbound drug concentration and increase the drug effect and, perhaps, produce toxicity.

When the amount of unbound drug in plasma increases, the rate of elimination will increase and after four half-lives the unbound concentration will return to its previous steady state value.

PHARMACODYNAMIC PRINCIPLES

A. Types of Drug-Receptor Interactions

AGONIST – drugs bind to and activate the receptor in some fashion, which directly or indirectly brings about the effect.

ANTAGONIST – by binding to a receptor, prevent binding by other molecules.

Partial agonist – bind to the same receptors and activate them in the same way but do not evoke as great a response, no matter how high the concentration.

Inverse agonist –is a ligand that binds to the same receptor-binding site as an agonist and not only antagonizes the effects of an agonist but exerts the opposite effect by suppressing spontaneous receptor signaling (when present).

- Most drugs must bind to a receptor to bring about an effect.

The Physical Nature of Drugs

To interact chemically with its receptor, drug molecule must have the:

Appropriate Size

Electrical Charge

Shape

The Physical Nature of Drugs (cont)

Atomic composition

FURTHERMORE...
A **useful drug** must have the necessary properties to be transported from its site of administration to its site of action.

A **practical drug** should be inactivated or excreted from the body at a reasonable rate so that its actions will be of appropriate duration.

DRUG - BODY INTERACTIONS

PHARMACODYNAMICS – the actions of the **drug on the body.** These determine the group in which the drug is classified

PHARMACOKINETICS – the actions of the **body on the drug.** Govern the **Absorption, Distribution, and Elimination** of drugs

2 BASIC PHARMACOKINETIC PARAMETERS:

VOLUME of DISTRIBUTION (V) - the measure of the apparent space in the body available to contain the drug. Relates the amount of drug in the body to the concentration of drug (C) in blood or plasma.

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2 BASIC PHARMACOKINETIC PARAMETERS: (cont)

CLEARANCE - the measure of the ability of the body to eliminate the drug. The factor that predicts the rate of elimination in relation to the drug concentration.

- The two major sites of drug elimination are the **kidneys and the liver.**
- Clearance of unchanged drug in the urine represents renal clearance.
- Within the liver, drug elimination occurs via **biotransformation**

Bioavailability

TABLE 3–3 Routes of administration, bioavailability, and general characteristics.

Route	Biovailability (%)	Characteristics
Intravenous (IV)	100 (by definition)	Most rapid onset
Intramuscular (IM)	75 to ≤100	Large volumes often feasible; may be painful
Subcutaneous (SC)	75 to ≤100	Smaller volumes than IM; may be painful
Oral (PO)	5 to <100	Most convenient; first-pass effect may be important
Rectal (PR)	30 to <100	Less first-pass effect than oral
Inhalation	5 to <100	Often very rapid onset
Transdermal	80 to ≤100	Usually very slow absorption; used for lack of first-pass effect; prolonged duration of action

The fraction of unchanged drug reaching the systemic circulation following administration by any route.

Pharmacokinetic Processes

Liberation	Applies to drugs given orally
	– Release of drug from pill, tablet, capsule
	– Dissolving of active drug in GI fluids
Absorption	Movement from administration site into circulation
Distribution	The transport of a drug in the body by the bloodstream to its site of action.
Metabolism	The biologic transformation of a drug into an inactive metabolite, a more soluble compound, or a more potent metabolite.
Excretion	- is the process by which a drug or metabolite is eliminated from the body.

Rate of Absorption

FIRST – ORDER KINETICS

- a constant fraction of drug is absorbed.

ZERO – ORDER KINETICS

- a constant amount of drug is absorbed.

The **blood brain barrier** consists of cell tightly packed around the capillaries of the CNS.

KIDNEY = most important organ for excretion of drugs.
= primary site

WHERE DO DRUG BIOTRANSFORMATIONS OCCUR?

• **Liver** is the principal organ of drug metabolism.

The 3 Major Types of Chemical forces or Bonds

COVALENT bonds – are very strong and in many cases not reversible under biologic conditions.

ELECTROSTATIC bonds – more common but are weaker than covalent bonds.

HYDROPHOBIC bonds – are usually quite weak and are important in the interactions of highly lipid soluble drugs.

Factors Influencing Absorption and Bioavailability

Aqueous diffusion of drug molecules is usually driven by the concentration gradient of the permeating drug, a downhill movement described by **Frick's law.**

Lipid diffusion - is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body.

Special Carriers – Special carrier molecules exist for certain substances that are important for cell function and **too large or too insoluble** in lipid to diffuse passively through membranes.

Endocytosis and Exocytosis:

ENDOCYTOSIS - is the process by which the substance is bound at a cell-surface receptor, engulfed by the cell membrane, and carried into the cell by pinching off of the newly formed vesicle inside the membrane.

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Endocytosis and Exocytosis: (cont)

EXOCYTOSIS - the reverse process. Is responsible for the secretion of many substances from cells.

For a drug to cross the lipid membrane easily / readily must have the ff. factors:
– Lipid soluble
– Uncharged
– Non polar
– Small in size
– Non ionized

THE TIME COURSE of DRUG EFFECT

Immediate Effects	drug effects are directly related to plasma concentrations.
Delayed Effects	Changes in drug effects are often delayed in relation to changes in plasma concentration.
Cumulative Effects	It is the accumulation of aminoglycoside in the renal cortex that is thought to cause renal damage.

Biological Half-life (t 1/2)

is the time required to change the amount of drug in the body by one-half during elimination.

the most useful in designing drug dosage regimens.

it indicates the time required to attain 50% of steady state—or to decay 50% from steady-state conditions

Drug Accumulation

With repeating drug doses, the drug will accumulate in the body until dosing ceases.

Accumulation: inversely proportional to the fraction of the dose lost in each dosing interval.

The **accumulation factor** predicts the ratio of the steady-state concentration to that seen at the same time following the first dose.

Hepatic 'First-Pass' Metabolism

• Affects orally administered drugs
• Drug absorbed into portal circulation, must pass through liver to reach systemic circulation
• May reduce availability of drug

Designing a Rational Dosage Regimen

MAINTENANCE DOSE

– Drugs are administered to maintain a steady state concentration in the body. (just enough drug is given in each dose to replace the drug eliminated since the preceding dose)

Clearance

is the most important pharmacokinetic term to be considered in defining a rational steady- state drug dosage regimen. – At steady state, the dosing rate ("rate in") must equal the rate of elimination ("rate out").

LOADING DOSE

Designing a Rational Dosage Regimen (cont)

– Promptly raises the concentration of drug in plasma to the target concentration.

Enzyme Induction & Inhibition

ENZYME INDUCTION	– Enhance the rate of drug`s synthesis or reducing its rate of degradation.
	– Induction results in an acceleration of substrate metabolism and usually in a decrease in the pharmacologic action of the inducer and also of coadministered drugs.
ENZYME INHIBITION	– Certain drug substrates inhibit cytochrome P450 enzyme activity.
	– Reduce the metabolism of the endogenous substrates or other coadministered drugs.

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