PRINCIPLES OF PHARMACOLOGY: An Overview

A. WHAT IS PHARMACOLOGY?

Pharmacology represents an integrated body of knowledge that deals with the actions of chemical and biologics on cellular functions.

1. Medical Pharmacology is the area of pharmacology that covers the use of drugs in the prevention (prophylaxis) and treatment of diseases.
2. Toxicology is the area of pharmacology concerned with the undesirable effects of chemicals and biologicals on cellular functions.
3. Pharmacology is the most integrated multidisciplinary science. It requires knowledge of all of the basic and clinical sciences to understand the mechanism of action of drugs.

B. MAJOR DRUG CLASSES FOR THE TREATMENT OF VARIOUS DISEASES

1. Autonomic drugs- These drugs target the autonomic system which is the major involuntary, unconscious autonomic portion of the nervous system.
   a. Cholinoceptor-activating and cholinesterase-inhibiting drugs
   b. Cholinoceptor blockers and cholinesterase regenerators
   c. Sympathomimetics
   d. Adrenoreceptor blockers

2. Cardiovascular drugs
   a. Antihypertensive agents
   b. Drugs used in the treatment of acute coronary syndrome
   c. Drugs used in the treatment of heart failure
   d. Anti-arrhythmic drugs
   e. Diuretic agents

3. Drugs effecting smooth muscle cells
   a. Histamine, serotonin and ergot alkaloids
   b. Vasoactive peptides
   c. Prostaglandins and their modulators
   d. Nitric oxide donors and inhibitors
   e. Bronchodilators
4. Drugs that act on the central nervous system
   a. Sedative/hypnotic drugs
   b. Alcohols
   c. Anti-seizure drugs
   d. General and local anesthetics
   e. Skeletal muscle relaxants
   f. Anti-parkinsonian drugs
   g. Anti-psychotic drugs
   h. Anti-depressant drugs
   i. Opioids analgesics and antagonists
   j. Drugs of abuse

5. Drugs with actions on blood, inflammation and gout
   a. Anti-anemia drugs and hematopoietic growth factors
   b. Drugs used in the management of thrombosis
   c. Anti-hyperlipidemic agents
   d. Non-steroidal anti-inflammatory agents

6. Endocrine drugs
   a. Hypothalamic and pituitary hormones
   b. Thyroid and anti-thyroid drugs
   c. Corticosteroids and antagonists
   d. Gonadal hormones and inhibitors
   e. Pancreatic hormones, anti-diabetics and hypoglycemic drugs
   f. Drugs that affect bone mineral homeostasis

7. Chemotherapeutic agents
   a. Antibiotics
b. Anti-fungal agents  
c. Anti-viral chemotherapy  
d. Antiprotozoal drugs  
e. Anti-helmentic drugs  
f. Cancer chemotherapy  
g. Immuno-modulators  

8. Drugs used in the treatment of gastrointestinal disorders  
9. Vaccines, complex biologic drugs and immune globulins  
10. Stem cell therapy  

C. **THE NATURE OF DRUGS**  
1. Inorganic ions  
2. Non-peptide organic molecular and organomimetics  
3. Small peptides and peptidomimetics  
4. Natural and recombinant proteins  
5. Nucleic acids and their analogues  
6. Lipids and lipid derived agents  
7. Carbohydrates and their derivatives  

The molecular weight of drugs varies from 7 daltons (Li\(^+\)) to > 100,000 daltons (antibodies, vaccines, enzymes)  

D. **ORIGIN AND SOURCE OF DRUGS**  
1. Microbes  
2. Plants  
3. Animals  
4. Inorganic elements and compounds  
5. Synthetic organic compounds  
6. Synthetic organomimetics
7. Biotechnology derived products
8. Biologics and products of human origin/recombinant equivalents

E. **DRUG FORMULATIONS**
1. Liquid
2. Tablets-
3. Suppositories
4. Sprays and inhalants
5. Ointments
6. Transdermal patches
7. Drug coating on medical devices (stents, catheters, extracorporeal circuits)
8. Drug implants
9. Micro and nanoparticles
10. Targeted drug delivery

F. **MOVEMENT (TRANSPORTATION) OF DRUGS IN THE BODY**
1. Aqueous diffusion
2. Lipid diffusion
3. Transport by special carriers
4. Endocytosis

G. **AQUEOUS AND LIPID SOLUTION OF DRUGS**
1. Aqueous diffusion
2. Lipid diffusion
   The pH of the medium determines the fraction of drugs charged (ionized) versus uncharged (non-ionized). If the pK, of the drug and pH on the medium are known, the ionized drug can be predicted by means of Henderson-Hasselbalch equation
3. Ionization of weak acids and bases
   \[ \text{RNH}_3^+ \leftrightarrow \text{RNH}_2^- + \text{H}^+ \]
\[ \text{RCOOH}^+ \leftrightarrow \text{RCOO}^- \ + \ \text{H}^+ \]

H. **ABSORPTION OF DRUGS**

1. Route of absorption
   a. Intravenous
   b. Intramuscular
   c. Subcutaneous
   d. Buccal and sublingual
   e. Rectal
   f. Inhalation
   g. Transdermal
   h. Other

2. Blood flow

2. Concentration

I. **DISTRIBUTION OF DRUGS**

1. Determinants of distribution
   a. Size of the target site (organ)
   b. Blood flow
   c. Solubility
   d. Binding

2. Apparent volume of distribution and physical volume

J. **METABOLISM OF DRUGS**

1. Drug metabolism as a mechanism of termination of drug action

2. Drug metabolism as a mechanism of drug activation

3. Drug elimination without metabolism

K. **ELIMINATION OF DRUGS**

1. First order elimination

   First order elimination implies that the rate of elimination is proportional to the concentration. The higher the concentration of drug the greater amount drug is eliminated per unit time.
2. **Zero order elimination**

Zero order elimination implies that the rate of elimination is constant regardless of the concentration.
L. **PHARMACOKINETIC MODELS**

1. **Multicomponent distribution**

Many drugs undergo an initial distribution phase followed by a slow elimination phase. Mathematically this process can be modeled by means of a two compartment model.

![Diagram of Zero-Order Elimination with plasma concentration over time](image)

Figure 2. Zero-order kinetics of drug elimination. The rate of elimination is constant and independent of circulating levels of the drug. (less common)
2. Single compartment distribution

A few drugs may behave as they are distributed to only one compartment (vascular compartment). Others have more complex distributions that require more than two compartments for construction of accurate models.

M. RECEPTORS FOR DRUGS

Drug effects result from their interactions with endogenous macromolecules in the patients that are called receptors. Upon interaction with the receptor, a drug can initiate biophysical and biochemical events leading to the observed drug effects. Drugs can bind to receptors with a variety of different bonds, which include covalent, electrostatic, and weaker bonds (hydrophobic, Van der Waals and hydrophilic).

1. Types of receptors
   a. Type I receptors: plasma membrane
      - Acetylcholine and norepinephrine
   a. Type II receptors: cytoplasm
      - Steroid hormones
   c. Type III receptors: nucleus
      - Anticancer drugs

2. Agonists: is a drug capable of fully activating the effector system when it binds to the receptor.
3. Antagonists: structural similarity to agonist and interact with receptor but does not cause same molecular change in receptor, therefore inhibits interaction of agonist with receptor.

4. Chain of events following a drug – receptor interaction

   \[ \text{Ach} + \text{receptor} \rightarrow \text{Na}^+ \text{ influx} \rightarrow \text{action potential} \rightarrow \text{increased free Ca}^{2+} \rightarrow \text{contraction} \]

   - Depends on particular receptor and particular type of cell.

5. Exceptions to drug actions mediated by specific receptors
   a. Volatile anesthetics
   b. Metal chelating agents
   c. Osmotic diuretics

6. Regulation of receptors
   a. Down-regulation (pharmacodynamic tolerance or desensitization): repeated administration of catecholamines decreasing number of alpha-receptors.
   b. Up-regulation (pharmacodynamic sensitization): thyroid hormone increasing number of beta-receptors in myocardium.

7. Receptor Changes In Diseases
   a. Antibodies to acetylcholine receptors in motor end-plates. Clinical application: Myasthenia gravis.
   b. Decreased number of receptors for plasma LDL (low density lipoproteins). Clinical application: Familial hypercholesterolemia.

N. **DRUG ANTAGONISMS**

1. Competitive antagonism: reversible competition for agonist receptor binding sites without inducing a biological response, such as:

2. Non-Competitive antagonism: Irreversible binding with receptor preventing agonist binding to receptor, such as DFP which combines with acetylcholinesterase to prevent acetylcholine from binding to acetylcholinesterase.

O. **DRUG NOMENCLATURE**

1. Type of drug names
   a. Chemical name: utilizes rules of organic chemistry.
   b. Code name: assigned to drug by pharmaceutical manufacturer.
   c. Generic name (nonproprietary name): if drug is admitted to United States Pharmacopoeia, the generic name becomes the official name of drug.
   d. Tradename (proprietary name) (trademark) (registered name): a superscript R or TM follows trade name.
      1) If drug is marketed by more than one pharmaceutical company, then the same drug may have several trade names but only one official generic name.

2. Use of generic or tradename of a drug
   a. Textbooks
   b. Lectures, handouts and examinations in this course
   c. National Board Examinations (USMLE)
   d. Prescription of drugs
1) A pharmacist may substitute a generic drug for a trade name drug unless the physician indicates "no substitution" on the prescription.
2) The physician can indicate the manufacturer for a generic drug.
3) Clinical application: Advantage of generic drugs is saving the patient money. Disadvantage of generic drugs is patient may receive a preparation of drug that is of inferior quality to a trade name drug.

e. Expressions of drug product equivalence related to generic drug substitution
1) Chemical equivalence: related to amount of drug per tablet.
2) Biological equivalence: related to pharmacokinetics involving bioavailability.
3) Therapeutic equivalence: related to clinical response that will provide same efficacy and toxicity (hopefully same lack of toxicity).
Clinical Application: very few generic drugs have been found to be therapeutically in equivalent to their trade name counterparts.

P. DRUG-TESTING AND APPROVAL

1. Pre-clinical testing and toxicology screen
2. Phase I: 10 normal volunteers receive small doses and observed for efficacy and safety
3. Phase II: Small group of patients with disease and observed for efficacy and safety
4. Phase III: large-scale clinical trial in patients with disease and observed for best dosage for treatment of disease.
5. NDA (New Drug application): If the FDA approves the NDA, then the drug goes on the market for general use.