PRINCIPLES OF PHARMACOLOGY: AN OVERVIEW

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WHAT IS PHARMACOLOGY?

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

3. Pharmacokinetics describes the effects of the body on drugs (absorption, distribution, metabolism, and excretion).

4. Pharmacodynamics describes the effects of drugs on the body (e.g., the mechanism of action, therapeutic and toxic effects).

WHAT IS PHARMACOLOGY?
MAJOR DRUG CLASSES FOR THE TREATMENT OF VARIOUS DISEASES

AUTONOMIC DRUGS

These drugs target the involuntary, unconscious portion of the nervous system.

a. Cholinoceptor-activating and cholinesterase-inhibiting drugs
b. Cholinoceptor blockers and cholinesterase regenerators
c. Sympathomimetics
d. Adrenoreceptor blockers

Drugs modulating the autonomic nervous system are used in a wide variety of indications.

CARDIOVASCULAR DRUGS

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

The mechanisms by which cardiovascular drugs mediate their therapeutic effects vary widely and include enzyme inhibition, receptor modulation and physiologic changes.
Aspirin is the most used cardiovascular drug in the world.

**ASPIRIN - THE WONDER DRUG**

Thrombolytics: Clot dissolving agents
Various agents will be covered in a separate lecture

**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

Potent musculotropic agents with both contractile and dilatation effects.
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. Opioid analgesics and antagonists
j. Drugs of abuse

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

Drugs with diverse mechanisms of action including hormonal, blood thinning and enzyme inhibitory effects.

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-diabetic and hyperglycemic drugs
f. Drugs that affect bone mineral homeostasis

Target endocrine sites by multiple mechanisms.
CHEMOTHERAPEUTIC AGENTS

a. Antibiotics
b. Anti-fungal agents
c. Anti-viral chemotherapy
d. Anti/protozoal drugs
e. Anti-helminthic drugs
f. Cancer chemotherapy
g. Immuno-modulators

A wide variety of drugs which can be used to control microbial infections, cancer cells and modulate the immune system.

DRUGS FOR GASTROINTESTINAL DISORDERS

1. Drugs used in acid-peptic diseases
2. Drugs stimulating GI motility
3. Laxatives
4. Anti-diarrheal agents
5. Anti-emetics

VACCINES, COMPLEX BIOLOGIC DRUGS AND IMMUNE GLOBULIN DRUGS

Active immunization – goal is 1º immune response with memory
- Whole killed bacteria
- Live attenuated bacteria/virus
- Bacterial polysaccharide (antigen)

Passive immunization – goal is short-term protection in specific populations
- Immunoglobulins
- Recombinant antibodies
Stem cell therapy is the use of stem cells to treat or prevent a disease or condition. Bone marrow transplant is a form of stem cell therapy that has been used for many years. No stem cell therapies other than bone marrow transplant are widely used. Stem cell therapies to treat various diseases, such as cancer, diabetes, and neurodegenerative disorders, are being clinically tested.
Monoclonal antibody therapy is a form of immunotherapy that uses monoclonal antibodies (mAb) to bind monospecifically to certain cells or proteins. This may then stimulate the patient's immune system to attack those cells.

### The Nature of Drugs

1. Inorganic ions
2. Non-peptide organic molecular and organonmimetics
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).
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

WHITE WILLOW TREE (SALIX ALBA VULGARIS), A NATURAL SOURCE OF SALICYLATES

ORIGIN OF NATURAL DRUGS

Protamine sulfate
Protamine
Penicillin
Hirudin: Thrombin inhibitor (65 amino acids)

Originally isolated from the leech. Now made by recombinant technology.

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 (antibody directed)

Vials and Ampules
Tablets
Gel capsules
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
3. Concentration

PATIENT RECEIVING CHEMOTHERAPY INFUSION

SUBCUTANEOUS INJECTION
TRANSDERMAL PATCH

MOVEMENT (TRANSPORTATION) OF DRUGS IN THE BODY

1. Aqueous diffusion
2. Lipid diffusion
3. Transport by special carriers
4. Endocytosis
AQUEOUS AND LIPID SOLUTIONS OF DRUGS

1. Aqueous diffusion
2. Lipid diffusion
   The pH of the medium determines the fraction drug which is charged (ionized) versus uncharged (non-ionized). If the pKₐ of the drug and pH on the medium are known, the amount of ionized drug can be predicted by means of Henderson-Hasselbalch equation.
3. Ionization of weak acids and bases
   \[ \text{RNH}_3^+ \rightarrow \text{RNH}_2 + \text{H}^+ \]
   \[ \text{RCOOH} \rightarrow \text{RCOO}^- + \text{H}^+ \]

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

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 metals, ions and inorganic compounds
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 of drug is eliminated per unit time.

FIRST ORDER ELIMINATION

Zero order elimination implies that the rate of elimination is constant regardless of the concentration.

ZERO ORDER ELIMINATION
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 a two compartment model]

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<table>
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</table>

Figure 3. Circulating levels of a drug after an intravenous bolus. The initial curvilinear portion of the data represents the distribution phase (α), whereas the linear portion of the curve represents the elimination phase (β).

PHARMACOKINETIC MODELS

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.
RECEPTORS FOR DRUGS

Drug effects result from their interactions with endogenous macromolecules 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 their receptors through a variety of different bonds, which include covalent, electrostatic and weaker bonds (hydrophobic, van der Waals and hydrophilic).

TYPES OF RECEPTORS

a. Type I receptors: plasma membrane
   - Acetylcholine and norepinephrine

b. Type II receptors: cytoplasm
   - Steroid hormones

c. Type III receptors: nucleus
   - Anticancer drugs
AGONIST
A drug capable of fully activating the effector system when it binds to the receptor.

ANTAGONIST
A drug with structural similarity to an agonist, but whose interaction with a receptor does not cause same molecular change in receptor, therefore, inhibits interaction of agonist with receptor.

CHAIN OF EVENTS FOLLOWING A DRUG-RECEPTOR INTERACTION
- Ach + receptor
- Na⁺ influx
- action potentials
- increased
- Free Ca²⁺
- contraction
- depends on particular receptor and particular type of cell
EXCEPTIONS TO DRUG ACTIONS MEDIATED BY SPECIFIC RECEPTORS

a. Volatile anesthetics
b. Metal chelating agents
c. Osmotic diuretics

REGULATION OF RECEPTORS

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

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
DRUG ANTAGONISMS: COMPETITIVE ANTAGONISM

Reversible competition for agonist receptor binding sites without inducing a biological response, such as naloxone to reverse opioid overdose and flumazenil which is an antidote to benzodiazepines.

DRUG ANTAGONISMS: 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.

DRUG NOMENCLATURE

TYPE OF DRUG NAMES

- Chemical name: utilizes rules of organic chemistry
- Code name: assigned to drug by pharmaceutical manufacturer
- Generic name (nonproprietary name): if a drug is admitted to the United States Pharmacopoeia, the generic name becomes the official name of the drug
- Tradename (proprietary name) (trademark) (registered name): a ® or ™ follows the tradename.
  - If a drug is marketed by more than one pharmaceutical company, then the same drug may have several trade names but only one official generic name
USE OF GENERIC OR TRADE NAME 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 tradename 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 patients may receive a preparation of drug that is inferior to the tradename drug.
EXPRESSION OF DRUG PRODUCT EQUIVALENCE: 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 lack of toxicity)

Clinical implications: most of the generic drugs are comparable in their safety and efficacy profile with the branded products. Very few exceptions.

DRUG-TESTING AND APPROVAL

1. Pre-clinical testing and toxicology screen.
2. Phase I: 10 normal volunteers receive small doses and observed for 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.

REVIEW QUESTION

The property that characterizes the effect of a drug on the body is called:

- Distribution
- Permeation
- Pharmacokinetics
- Pharmacodynamics
- Elimination
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REVIEW QUESTION

The anticoagulant drug heparin is obtained from which of the following source:
- a. Bovine and porcine intestine tissues
- b. Recombinant protein technology
- c. Bark of the white willow tree
- d. Salmon fish
- e. Mushroom
HAVE A GOOD SECOND YEAR