

Introduction to Clinical Pharmacology

Chapter 1 General Principles of Pharmacology

Introduction to Pharmacology

Pharmacology: study of drugs, their action on living organisms

Sound knowledge of basic pharmacologic principles

- Enables safe medicine administration and monitoring of patients



Drug Names and Categories

Categories: chemical; generic; nonproprietary; official; trade or brand name

Several trade names: use generic name to avoid confusion

After drug approval FDA assigns categories:

- **prescription**
- **nonprescription**
- **controlled substance**

Question #1

What occurs during Phase 2 of clinical drug development?

- A. 20 to 100 volunteers involved to see what drug does to health tissue
- B. Test performed on people having the disease for which drug might be effective
- C. Drug given to large numbers of patients in medical research centers that provided information about adverse reactions

Answer to Question #1

- B
- Phase 1: 20 to 100 volunteers involved to see what drug does to healthy tissue
- Phase 2: test performed on people having the disease for which drug might be effective
- Phase 3: drug given to large numbers of patients in medical research centers that provided information about adverse reactions
- Phase 4: postmarketing surveillance

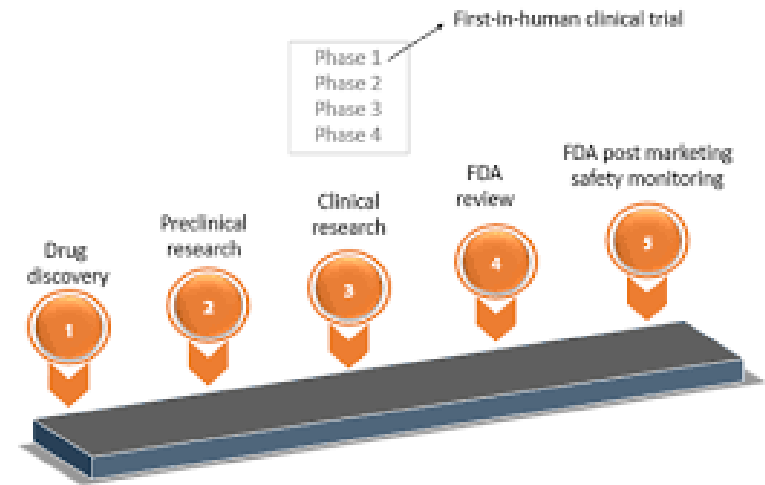
Drug Development #1

Process of drug development: long and arduous—7 to 12 years or longer

FDA: approves new drugs, monitors current drugs—adverse/toxic reactions

Development of drug:

- pre-FDA phase
- FDA phase



Drug Development #2

Clinical testing: four phases

- Phase 1: 20 to 100 volunteers involved to test drug on health tissue
- Phase 2: test performed on people having the disease for which drug might be effective
- Phase 3: drug given to large numbers of patients in medical research centers for information about adverse reactions

Drug Development #3

Phase 4: postmarketing surveillance

- Ongoing review: particular attention to adverse reactions

Health care professionals: help with surveillance; report adverse effects to FDA using MedWatch



Question #2

Is the following statement true or false?

Orphan Drug Act: passed to encourage development and marketing of products for common diseases

Answer to Question #2

False

Orphan Drug Act: passed to encourage development and marketing of products for rare diseases, not common diseases

Orphan Drug Program

Orphan Drug Act: passed to encourage development and marketing of products for rare diseases

Rare disorders: Tourette syndrome; ovarian cancer; amyotrophic lateral sclerosis

Drug approved: manufacturer gets 7 years of exclusive marketing rights

Orphan drugs: Velcade for amyloidosis; enzyme replacement therapy for Gaucher disease; atiprimod for multiple myeloma

Accelerated Programs

Accelerated approval/provisional approval

Diseases that are a threat to public health:
AIDS—considered for shorter IND approval process

Allows primary care providers to administer medications with positive results in early Phase 1 and 2 clinical trials

Waiting until final approval not required: drug continues to prove beneficial—process of approval accelerated

Drug Activity Within the Body

Drugs: act in various ways in the body

Oral drugs: three phases

- Pharmaceutical: dissolution of drug occurs; drugs must be soluble to be absorbed
- Pharmacokinetic: absorption; distribution; metabolism; excretion
- Pharmacodynamics: deals with drugs action and effect on body

Pharmaceutical Phase

Liquid and parenteral drugs: already dissolved—quickly absorbed

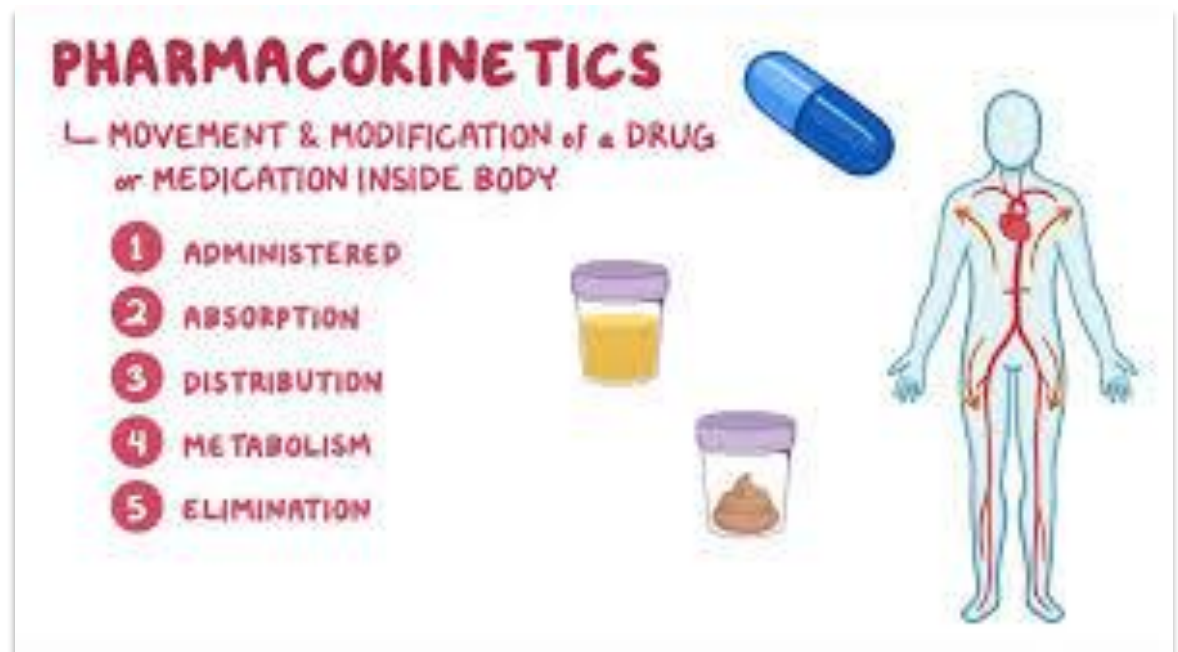
Solid forms of drugs: tablets or capsules—disintegrate into small particles; dissolve into body fluids in GI tract

Enteric-coated tablets: disintegrate after reaching alkaline environment of small intestine

Pharmacokinetic Phase

Pharmacokinetics: activities within the body after a drug is administered

- Absorption
- Distribution
- Metabolism
- Excretion



Absorption

Drug particles within gastrointestinal tract: move into body fluids

Factors influencing rate of absorption: route of administration; solubility of drug

First-pass effect: drug absorbed by small intestine; liver first metabolizes drug; remaining drug not sufficient to produce therapeutic effect

- patient needs higher dosage for desired effect



Distribution

Systematic circulation: drug distributed to various body tissues and target sites—interact with specific receptors in body

Factors affecting distribution: protein binding (free/bound drugs); blood flow; solubility (lipid-soluble drugs/water-soluble drugs)

Quick distribution: heart; liver; kidneys

Slow distribution: internal organs; skin; muscle

Metabolism and Excretion

Metabolism: body changes drug to a more or less active form for excretion

Excretion: elimination of drugs from the body

Patients with kidney disease: require dosage reduction and careful monitoring of kidney function

Older adults: diminished kidney function—require careful monitoring and lower dosages

Half-Life

Time required for the body to eliminate 50% of the drug

Drugs with short half-life: administered frequently

Drugs with long half-life: require less frequent dosing

Difficulty in drug excretion: increases half-life and risk of toxicity

Onset, Peak, and Duration

Onset of action: time between drug administration and beginning of therapeutic effect

Peak concentration: absorption rate equals elimination rate

Duration of action: time for drug to produce therapeutic effect

Pharmacodynamic Phase

Pharmacodynamics: study of drug mechanisms producing biochemical/physiologic changes in body

Primary effect of drug: desired or therapeutic effect

Secondary effect of drug: other desirable or undesirable effects

Drugs exert action—two mechanisms: alteration in cellular form/environment

Alteration in Cellular Environment

Physical changes: osmotic pressures; lubrication; absorption; conditions—surface of cell membrane

- Mannitol; sunscreen; activated charcoal; docusate

Chemical changes: inactivation of cellular functions; alteration of chemical components of body fluid—change in the pH

- Antacids; cancer drugs or some antibiotics

Receptor-Mediated Drug Action

Drug interacts with receptor; function of a cell alters; drug molecule joins with reactive site (receptor) on surface of cell

Agonist: binds with and stimulates receptor—therapeutic response

Antagonist: joins with but does not stimulate receptors; prevents drug response; competitive/noncompetitive

Effects of number of available receptor sites; potent drugs

Drug Use and Pregnancy

Drugs administered during the first trimester:
may cause teratogenic effects

Most drugs: contraindicated unless benefits outweigh risk

Pregnant women: use drugs/herbal supplements only after consultation

Risks of smoking and drinking: low birth weight; premature birth; fetal alcohol syndrome

Addictive drugs: children born with addiction

Various Drug Reactions

Allergic drug reactions

Drug idiosyncrasy

Drug tolerance

Cumulative drug effect

Toxic reactions

Pharmacogenetic reactions

Allergic Drug Reactions (Hypersensitivity Reactions)

Usually begin after more than one dose of the drug is given; body views drug as antigen

Signs and symptoms: itching; skin rashes; hives; wheezing; cyanosis; sudden loss of consciousness; swelling of eyes, lips, or tongue

Anaphylactic shock; hypotension and shock; angioedema

Drug Idiosyncrasy

Unusual, abnormal reaction to drug; different from expected reaction

Cause: believed to be due to genetic deficiency

Drug Tolerance

Decreased response to a drug: requires increased dosage for desired effect

Example: narcotics or tranquilizers taken for a long time

Cumulative Drug Effect

Patients with liver and kidney disease: body is unable to metabolize and excrete one dose of drug before next dose is given

Dose lowered to prevent toxic drug reaction

Toxic Reactions

Drug is administered in large dosages; blood concentration levels exceed therapeutic levels

Reverse drug toxicity: Administer another drug as antidote; monitor drugs with low safety margin

Pharmacogenetic Reactions

Pharmacogenetic disorder

- Genetically determined abnormal response to normal doses of a drug
- Inherited traits cause abnormal metabolism of drugs

Patients with G6PD deficiency: Drugs cause hemolysis (aspirin; chloramphenicol; sulfonamides)

Drug Interactions

One drug interacts and interferes with the action of another drug

- Oral anticoagulants; oral hypoglycemics; anti-infectives; antiarrhythmics; cardiac glycosides; alcohol

Effects: Additive; synergistic; antagonistic

Additive Drug Reaction

Combined effect of two drugs is equal to sum of each drug given alone ($1 + 1 = 2$)

Synergistic Drug Reaction

Drugs interact with each other and produce a sum greater than the sum of their separate actions ($1 + 1 = 3$)

Antagonistic Drug Reaction

One drug interferes with action of
another: neutralization/decrease in effect
of one drug

Drug–Food Interactions

Food may impair or enhance drug's absorption

- Drug taken on empty stomach (captopril)
- Drugs that irritate stomach; cause nausea, vomiting, epigastric distress: given with meals (anti-inflammatory drugs; salicylates)
- Drug–food mixture: drugs combine with a food forming an insoluble food (tetracycline administered with dairy products)

Question #3

Is the following statement true or false?

Age is a factor that influences drug response.

Answer to Question #3

True

Age, weight, gender, disease, and route of administration are factors influencing drug response.

Factors Influencing Drug Response

Age

Weight

Gender

Disease

Route of administration

Nursing Implications

Consult appropriate references and hospital pharmacist

Observe patients

Report

Use judgment

Accurately observe and evaluate circumstances

Record

Herbal Therapy and Dietary Supplements

Herbal therapy

- Type of complementary/alternative therapy—using plants or herbs
- Explain that “natural” is not necessarily safe

Nutritional or dietary supplements

- Substances not regulated as drugs by FDA; effective for promoting health