Pharmacology

General Principles

NAPNES Guidelines

Unit I

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Pharmacology Defined

- Study of drug's actions on living organisms
  - Drug
    - Any chemical that affects the processes of a living organism
- Drug development
  - ~ 7 -12 years or longer
  - FDA approval necessary for all drugs
- Compassionate access to unapproved drugs
  - Allows certain pts to receive drugs w/o FDA approval

Drug Development

- ***Preclinical Testing***
  - A pharmaceutical company conducts laboratory and animal studies
    - to show biological activity of the compound against the targeted disease
    - evaluated for safety
    - take approximately three and one-half years
- ***Investigational New Drug Application (IND)***
  - After completing preclinical testing
    - the company files an IND with FDA to begin to test the drug in people
      - becomes effective if FDA does not disapprove it within 30 days.
      - shows results of previous experiments
        - » how, where and by whom the new studies will be conducted
        - » the chemical structure of the compound
        - » how it is thought to work in the body
        - » any toxic effects found in the animal studies
        - » how the compound is manufactured

Drug Development (cont.)

- ***Clinical Trials***
  - ***Phase I***
    - These tests take about a year
    - involve about 20 to 80 normal, healthy volunteers
    - study a drug's safety profile, including the safe dosage range
    - determine how a drug is absorbed, distributed, metabolized and excreted, and the duration of its action

Drug Development (cont.)

- ***Clinical Trials (cont.)***
  - ***Phase II***
    - controlled studies of approximately 100 to 300 volunteer patients (people with the disease) assess the drug's effectiveness
    - take about two years
  - ***Phase III***
    - lasts about three years
    - usually involves 1,000 to 3,000 patients in clinics and hospitals
    - physicians monitor patients closely to determine efficacy and identify adverse reactions.

Drug Development (cont.)

- ***New Drug Application (NDA)***
  - following the completion of all three phases of clinical trials
  - the company analyzes all of the data and files an NDA with FDA if the data successfully demonstrate safety and effectiveness
  - the NDA must contain all of the scientific information that the company has gathered
    - typically run 100,000 pages or more
    - by law, FDA is allowed six months to review an NDA.

Drug Development (cont.)

- ***Approval***
  - Once FDA approves the NDA, the new medicine becomes available for physicians to prescribe.
  - The company must continue to submit periodic reports to FDA
    - including any cases of adverse reactions and appropriate quality-control records
    - for some medicines, FDA requires additional studies (Phase IV) to evaluate long-term effects.
  - Cost
    - $12.6 billion in research and development
      - has been doubling every five years.

Pharmacologic Principles

- Pharmaceutics
- Pharmacokinetics
- Pharmacodynamics
- Pharmacotherapeutics
- Taxicology
- Pharmacognosy

Pharmacologic Principles (cont.)

Pharmaceutics

- Dissolution of the drug
- Tablets of capsules
  - Disintegrates into small particles
  - Dissolves into body fluids within GI tract
- Drugs that are liquid of given by injection do not go through this phase.

Pharmacologic Principles (cont.)
Pharmaceutics

- Drug Absorption of Various
  - –Oral Preparations

Liquids, elixirs, syrups	Fastest
Suspension solutions	↓
Powders	↓
Capsules	↓
Tablets	↓
Coated tablets	↓
Enteric-coated tablets	Slowest

Pharmacologic Principles (cont.)

Pharmacokinetics

- The study of what the body does to the drug:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Pharmacologic Principles (cont.)

Pharmacokinetics

- Absorption
  - Occurs after dissolution of drug
  - Drug → GI tract → body fluids → tissue

Pharmacologic Principles (cont.)

Pharmacokinetics; *Absorption*

Factors That Affect Absorption

- Administration route of the drug
- Food or fluids administered with the drug
- Dosage formulation
- Status of the absorptive surface
- Rate of blood flow to the small intestine
- Acidity of the stomach
- Status of GI motility

Pharmacologic Principles (cont.)

Pharmacokinetics; *Absorption*

Routes

- A drug's route of administration affects the rate and extent of absorption of that drug.
  - Enteral
  - Parenteral
  - Topical

Pharmacologic Principles (cont.)

Pharmacokinetics; *Absorption*

Enteral Route

- Drug is absorbed into the systemic circulation through the oral or gastric mucosa, the small intestine, or rectum.
  - Oral
  - Sublingual
  - Buccal
  - Rectal

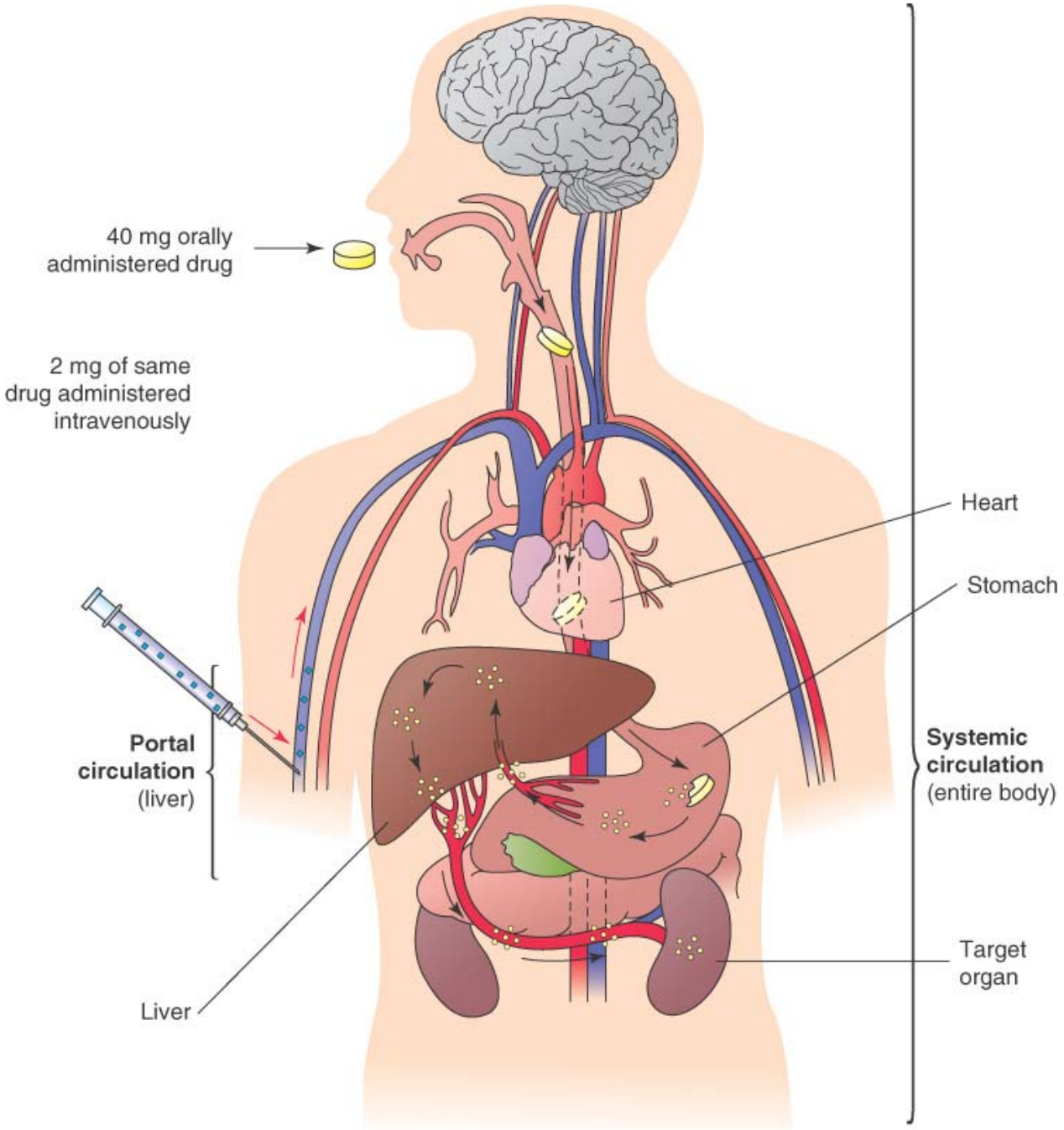
Pharmacologic Principles (cont.)

Pharmacokinetics; *Absorption*

First-Pass Effect

The metabolism of a drug and its passage from the liver into the circulation.

- A drug given via the oral route may be extensively metabolized by the liver before reaching the systemic circulation (high first-pass effect).
- The same drug—given IV—bypasses the liver, preventing the first-pass effect from taking place, and more drug reaches the circulation.



Pharmacologic Principles (cont.)

Pharmacokinetics; *Absorption*

- Routes that bypass the liver:
  - Sublingual
  - Buccal
  - Rectal*
  - Intravenous
  - Intranasal
  - Transdermal
  - Vaginal
  - Intramuscular
  - Subcutaneous
  - Inhalation

  *Rectal route undergoes a higher degree of first-pass effects than the other routes listed.

Pharmacologic Principles (cont.)
Pharmacokinetics; *Absorption*

Parenteral Route

- Intravenous*
- Intramuscular
- Subcutaneous
- Intradermal
- Intrathecal (physician)
- Intraarticular (physician)

*Fastest delivery into the blood circulation

Pharmacologic Principles (cont.)

Pharmacokinetics; *Absorption*

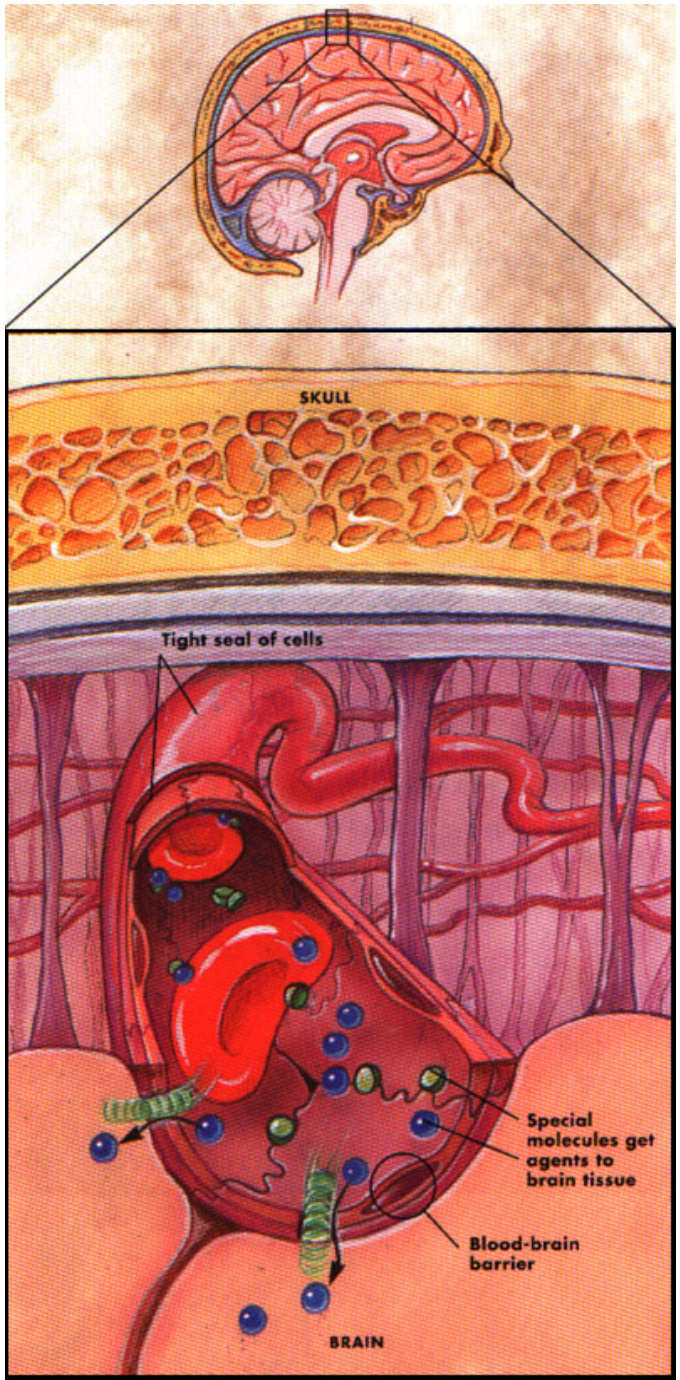
Topical Route

- Skin
- Eyes
- Ears
- Nose
- Lungs (inhalation)
- Vagina

Pharmacologic Principles (cont.)

Pharmacokinetics; *Distribution*

- Systemic circulation distributes drugs to various body tissues or target sites
- Most drugs travel by binding to proteins
  - Protein releases drug at target site
  - Diffuses into tissue
  - Interact with receptor
  - Produce therapeutic effect
- Therapeutic level
  - Level of drug to maintain desired effect



The tight seal of cells that lines the blood vessels in the brain is known as the blood-brain barrier. Researchers are trying to sneak therapies past the barrier to the brain tissue by hitching therapeutic agents onto molecules that already are allowed to slip through or with compounds that pry open the seals

Pharmacologic Principles (cont.)

Pharmacokinetics; *Metabolism*

- aka biotransformation
- Process which a drug is converted by liver to inactive compounds, a more soluble compound, or a more potent metabolite.
  - Series of chemical reactions
- Kidneys, lungs, plasma and intestinal mucosa also aid in metabolism

Pharmacologic Principles (cont.)
Pharmacokinetics; *Metabolism*

Factors that decrease metabolism:

- Cardiovascular dysfunction
- Renal insufficiency
- Starvation
- Obstructive jaundice
- Certain drugs
  - Erythromycin or ketoconazole drug therapy

Factors that increase metabolism:

- Certain drugs
  - Barbiturates
  - Rifampin therapy

Pharmacologic Principles (cont.)
Pharmacokinetics; *Metabolism*

Delayed drug metabolism results in:

- Accumulation of drugs
- Prolonged action of the effects of the drugs

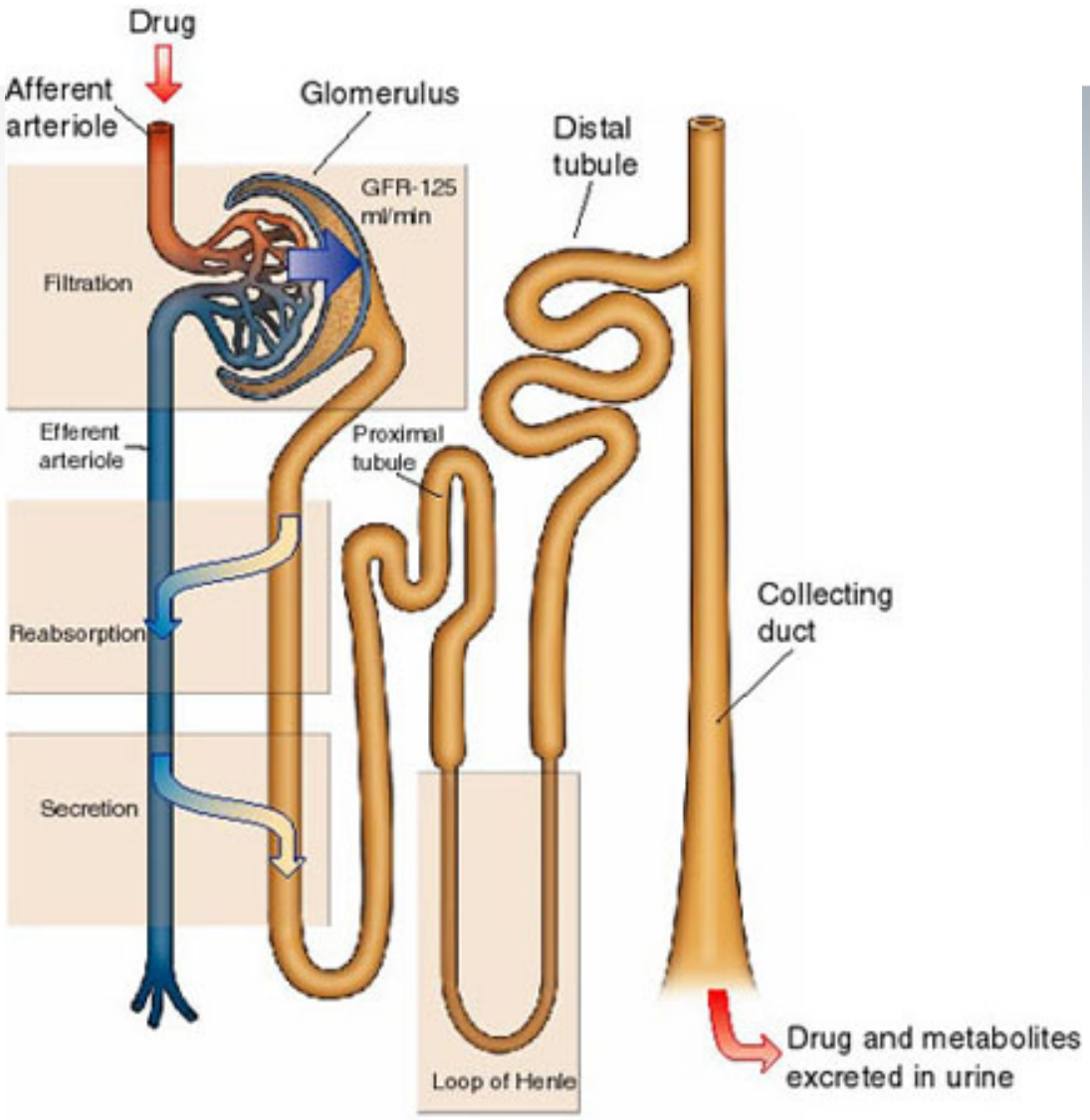
Stimulating drug metabolism causes:

- Diminished pharmacologic effects

Pharmacologic Principles (cont.)

Pharmacokinetics; *Excretion*

- Elimination of drug form the body
- Kidney excrete inactived (by liver) drug/compounds
  - Some drugs may be excreted unchanged by the liver
- Sweat, breast milk, breath or GI tract (feces)
  - Also eliminate drug


Drug
Afferent arteriole
Glomerulus
Distal tubule
GFR-125 ml/min
Filtration
Efferent arteriole
Proximal tubule
Reabsorption
Collecting duct
Secretion
Loop of Henle
Drug and metabolites excreted in urine

Pharmacologic Principles (cont.)

Pharmacokinetics; *Half-Life*

- Time required to eliminate 50% of a drug
- Takes 5 – 6 half-lives to eliminate ~ 98% of a drug
- Liver or kidney disease
  - Can prolong half-life
  - Increases risk of toxicity

Pharmacologic Principles (cont.)

Pharmacokinetics; *Half-Life*

The Concept of Drug Half-Life

DIFFERENT PERSPECTIVES	CHANGING VALUES					
Drug concentration (mg/L)	100	50	25	12.5	6.25	3.125
Hours after peak concentration	0	8	16	24	32	40
Number of half-lives	0	1	2	3	4	5
Percentage of drug removed	0	50	75	88	94	97

Pharmacologic Principles (cont.)

Pharmacokinetics; *Onset, Peak, Duration*

Onset

- The time it takes for the drug to elicit a therapeutic response

Peak

- The time it takes for a drug to reach its maximum therapeutic response

Duration

- The time a drug concentration is sufficient to elicit a therapeutic response

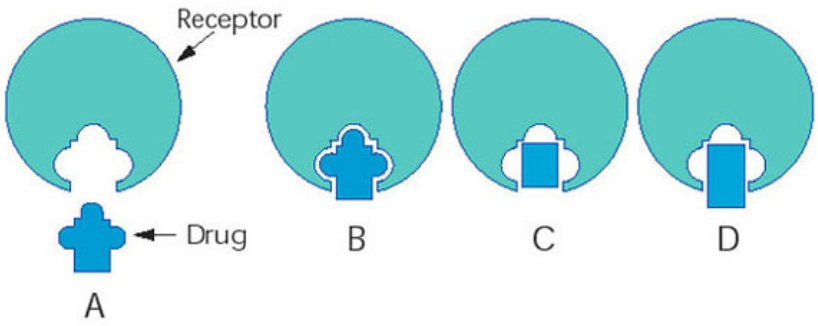
Pharmacologic Principles (cont.)
Pharmacodynamics

- **Pharmacodynamics**
  - Deals with *drug's action & effect* within body
  - Almost all body tissues exposed to drug
  - Most drugs produce more than one effect
    - Therapeutic effect – desired or primary effect
    - Secondary effect – may be desirable or not
- Target sites
  - *Drug effect* usually at cellular level at these sites by altering:
    - Cellular function
      - Receptor-mediated drug action
      - Enzyme-mediated drug action
    - Cellular environment
      - Physically
      - Chemically

Pharmacologic Principles (cont.)

Pharmacodynamics; *Alteration in Cellular Function*

- Receptor-Mediated Drug Action
  - Drug binds to specific receptor
    - Alters cell function
    - Produces desired effect
    - Can bind completely or partially
  - ***Agonists***
    - Drugs that bind and produce desired effect
  - ***Antagonist***
    - Drugs that block agonist effect at binding site



Drug-Receptor Interactions: Definitions

INTERACTION TERM	DEFINITION
Agonist	Drug binds to receptor, and there is a response.
Partial agonist	Drug binds to receptor, and there is a diminished response compared with that elicited by the agonist.
Antagonist	Drug binds to receptor, but there is no response. Drug prevents binding of agonists.
Competitive antagonist	Drug competes with the agonist for binding to receptor. If it binds, there is no response.
Noncompetitive antagonist	Drug combines with different parts of receptor and inactivates it, so agonist has no effect.

Pharmacodynamic Phase
Alteration in Cellular Function (cont.)

- Receptor-Mediated Drug Effects
  - Depends on
    - # of receptors on cell
    - Potency of drug
    - Amount of drug

Pharmacodynamic Phase
Alteration in Cellular Function (cont.)

- Enzyme mediated drug action
  - Drug interacts with enzyme system
    - Inhibits the action of the enzyme
    - The action of the cell is blunted or altered

Pharmacologic Principles (cont.)

Pharmacodynamics; *Alteration in Cellular Environment*

Nonspecific drug interactions:

- Drugs change the cellular environment
  - Physically
    - Osmotic pressure
    - Lubrication
    - Absorption
    - Conditions on the surface of cell membrane
  - Chemically
    - Inactivation of cellular functions
    - Alterations of the chemical component in body fluids

Poisoning Treatment

- Call local poison control center or 911
  - Recommended before giving any antidote
- Syrup of ipecac
  - No longer recommended
  - Never use unless instructed by a medical professional
- Activated charcoal
  - First-line treatment
  - Not effective for alcohol, caustics, lithium, or petroleum products.

Pharmacologic Principles (cont.)

Pharmacotherapeutics

- The treatment of pathologic conditions through the use of drugs
  - Empirical
  - Rational
- Desired therapeutic outcome
  - Should be established before initiation of drug therapy
    - Must be measurable and realistic

Pharmacologic Principles (cont.)

Pharmacotherapeutics

- Types of therapy
  - Acute
  - Maintenance
  - Supplemental
  - Palliative
  - Supportive
  - Prophylactic and Empiric

Pharmacologic Principles (cont.)

Pharmacotherapeutics

- Acute therapy
  - Involves more intensive drug therapy
  - Used in the acutely or critically ill
  - Usually needed to maintain life
- Maintenance therapy
  - Usually does not eradicate problem
    - May prevent progression
  - Used in chronic illnesses (i.e., hypertension)

Pharmacologic Principles (cont.)

Pharmacotherapeutics

- Supplemental therapy
  - Replaces body substances needed to maintain normal functioning
    - May not be produced by the body
    - Produced in insufficient amounts
- Palliative therapy
  - Goal is to provide comfort
  - Used in end stage illnesses
  - Usually all other therapy has failed

Pharmacologic Principles (cont.)

Pharmacotherapeutics

- Supportive therapy
  - Maintains the integrity of body functions while patient recovering from certain illnesses
  - Examples
    - Providing fluids/electrolytes to prevent dehydration
      - In vomiting or diarrhea
    - Blood products or volume expanders
      - Blood loss during surgery

Pharmacologic Principles (cont.)

Pharmacotherapeutics

- Prophylactic therapy
  - Based on practical experience or scientific knowledge
- Empiric therapy
  - Administration of drug when a certain pathological process is suspected on the basis of patient's symptoms
    - Also based on past experience
    - Acetaminophen for fever
      - Cause of fever unknown
      - But known to decrease fever

Pharmacologic Principles (cont.)

Toxic Effects - Monitoring

- Therapeutic Index
  - Ratio of a drug's therapeutic benefits to its toxic effects
    - Determines safety of a drug
    - Narrow therapeutic index
      - Greater likelihood than other drugs of causing adverse effects
        - » Closer monitoring
      - Examples
        - » Warfarin
        - » Digoxin

Pharmacologic Principles (cont.)

Toxic Effects - Monitoring

- Drug concentration
  - Monitored by blood levels
  - Can correspond to either
    - therapeutic response
    - toxic level
      - Commonly occurs with impaired liver/kidney function

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition - Physiological

- Age
  - Infants & children need ↓ dose
    - Immature organ function
  - Elderly may require ↓ dose
    - Decreased gastric acidity
    - Dry mouth/decreased saliva
    - Decreased liver blood flow/mass
    - Decreased skin lipid content
    - Increased body fat, decrease body water
    - Decreased serum proteins
    - Decreased kidney function
    - Changes in sensitivity to certain drug receptors

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition - Physiological

- Weight
  - Average = 150lb
  - Dosage adjustments
    - Large weight differences
- Gender
  - Women
    - Smaller
    - Different fat/water ratio

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition - Physiological

- Drug Idiosyncrasy/Individual variation
  - Any abnormal/unusual reaction to a drug
  - Cause not clear
    - ? Genetic tendency
  - Example
    - Sleeping pill makes pt more awake
    - Sedation with a stimulant drug

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition - Pathological

- Liver/kidney disease
  - Inability to metabolize/excrete one normal dose before next drug given
  - Leads to drug toxicity
  - Lower doses are frequently given
    - Liver disease
    - Kidney disease

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition – Psychological

- Emotional state of patient
- Effect of nurse's attitude
- Use of placebo
- Environment

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition – Genetic

- Enzyme systems
  - Genetically determined abnormal response
    - Causes abnormal metabolism of drug
  - Example
    - G6PD deficiency
      - Varying degrees of hemolysis
      - ASA, chloramphenicol, sulfonamides

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition – Genetic

- Tachyphylaxis
  - ↓ drug response
  - Requires ↑ dose to get effect
  - Sign of drug dependence
  - Narcotics/tranquilizers most common drugs

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Patient's condition – Genetic

- Hypersensitivity (Allergic Drug Reactions)
  - Usually begins after > one dose
  - May occur within minutes or delay for hours or even days
  - s/s = skin rashes, hives (uticaria), difficulty breathing, sudden LOC, facial swelling etc.
  - **Anaphylactic Shock**
    - Severe allergic rx
  - Angioedema (angioneurotic edema)
    - Collection of fluid in subQ tissue

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Tolerance & Dependence

- Tolerance
  - Decreasing response to repetitive drug doses
- Dependence
  - Physiologic or psychological need for a drug
    - Physical
      - i.e., opiod for cancer patient
    - Psychological
      - i.e., desire for the euphoric effect of a drug
        - » Narcotics, benzodiazepines, amphetamines
        - » Recreational drugs

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Drug Interactions

- Drug – Drug Interactions
  - Additive drug reaction
  - Synergistic drug reaction
  - Antagonistic drug reaction
- Drug – Food Interactions
- Incompatibility
  - Term commonly used with parenteral drugs
    - Mixture of two drugs/solutions resulting in a chemical deterioration of one or both of the drug
      - Produces
        - » Precipitate, haziness, or color change
        - » Example is IV Lasix & Heparin

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Drug Interactions

TABLE 2-8

EXAMPLES OF DRUG INTERACTIONS AND THEIR EFFECTS ON PHARMACOKINETICS

Pharmacokinetic Phase	Drug	Mechanism	Result
Absorption	Antacids with ketoconazole	Increases gastric pH, preventing the breakdown of ketoconazole	Decreased effectiveness of ketoconazole, resulting from decreased blood levels (harmful)
Distribution	warfarin with amiodarone	Both drugs compete for protein-binding sites	Higher free, unbound warfarin and amiodarone, increasing actions of both drugs (harmful)
Metabolism	erythromycin with cyclosporine	Both drugs compete for the same hepatic enzymes	Decreased metabolism of cyclosporine, possibly resulting in toxic levels of cyclosporine (harmful)
Excretion	amoxicillin with probenecid	Inhibits the secretion of amoxicillin into the kidneys	Elevates and prolongs the plasma levels of amoxicillin (can be beneficial)

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Other Drug Effects

- Teratogenic Effects
  - Teratogen
    - Any substance that causes abnormal development of the fetus leading to a severely deformed fetus
      - Viral diseases, radiation & drugs/chemicals (***drug-induced teratogenesis***)
  - FDA established 5 categories (A,B,C,D,X) suggesting potential of teratogenic effects
    - Category A = studies show no risk
    - Category X = contraindicated in pregnancy
      - Fetal risk outweighs any possible benefit to pt

DISPLAY 1-3 • Pregnancy Categories

PREGNANCY CATEGORY A

- Controlled studies show no risk to the fetus.
- Adequate well-controlled studies in pregnant women have not demonstrated risk to the fetus.

PREGNANCY CATEGORY B

- There is no evidence of risk in humans.
- Animal studies show risk, but human findings do not.
- If no adequate human studies have been done, animal studies are negative.

PREGNANCY CATEGORY C

- Risk cannot be ruled out.
- Human studies are lacking, and animal studies are either positive for fetal risk or lacking.
- The drug may be used during pregnancy if the potential benefits of the drug outweigh its possible risks.

PREGNANCY CATEGORY D

- There is positive evidence of risk to the human fetus.
- Investigational or postmarketing data show risk to the fetus.
- However, potential benefits may outweigh the risk to the fetus. If needed in a life-threatening situation or a serious disease, the drug may be acceptable if safer drugs cannot be used or are ineffective.

PREGNANCY CATEGORY X

- Use of the drug is contraindicated in pregnancy.
- Studies in animals or humans or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

Regardless of the pregnancy category or the presumed safety of the drug, no drug should be administered during pregnancy unless it is clearly needed and the potential benefits outweigh potential harm to the fetus.

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Other Drug Effects

- Mutagenic Effects
  - Permanent changes in genetic composition
    - Alteration of
      - chromosome structure
      - Number of chromosome
      - Genetic code of the DNA molecule
  - Mutagens
    - Agents capable of producing mutations
    - Radiation, chemicals and drugs are examples
- Iatrogenic Effects
  - Unintentional adverse effects
    - Induced by health care provider or treatment

Pharmacologic Principles (cont.)

Toxic Effects – Monitoring

Other Drug Effects

- Carcinogenic Effects
  - Carcinogens
    - Drugs/chemicals that cause cancer
  - Usually requires prolonged exposure
  - Potent carcinogens
    - May require brief exposures, but
    - Involve long latent period before cancer develops

Pharmacologic Principles (cont.)

Pharmacognosy

- The study of natural drug sources
  - Plants
  - Animals
- Four main sources of drugs
  - Plants
  - Animals
  - Minerals
  - Laboratory synthesis

Pharmacologic Principles (cont.)

Herbal Therapy/Nutritional Supplements

- Botanical medicine
- Herbal therapy
- Complementary/alternative medicine (CAM)
- Most not scientifically tested/regulated by FDA
  - Safety/efficacy
  - Regulated as nutritional supplement

Drug Names

- Chemical name
  - Exact chemical structure, not capitalized
  - Example: ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cycloheptal[1,2-b]-pyridin-11-ylidene)-1-piperidinecardisplayylate
- Generic name
  - Name given before official, not capitalized
  - Used by all countries & manufacturers
  - Example: loratadine

Drug Names (cont.)

- Official name
  - Name listed in *The United State Pharmacopeia-National Formulary*
  - May be same as generic name
  - Example: loratadine
- Trade (Brand) name
  - Name registered by manufacturer, capitalized
  - Followed by manufacturer symbol
  - Single drug may have several brand names
    - Depending on # of manufacturers
  - Example: Claritan©

Drug Classifications

- Place drugs in similar categories
  - Similar general use
  - Similar mechanisms of actions
  - Similar contraindications
  - Similar precautions
  - Similar nursing implications

Drug Classifications (cont.)

- Examples:
  - Antidiarrheals
  - Antiepileptics
  - Sedatives
  - Anesthetics
  - Decongestants
  - Antineoplastics

Drug References

- Physicians Desk Reference (PDR)
- U.S. Pharmacopia
- National Formulary
- Various Nursing Drug Handbooks/References
  - Davis Drug Guide

Drug Card Sample (Side 1)

Generic Name: Ibuprofen **Pharm. Class.:** non-opioid analgesic

Brand Name: Advil, Motrin, Nuprin, others

Usual Dosage/Route of administration : Adults: 400-800mg 3-4 times daily po, not to exceed 3600mg/day

Mechanism of Action: Inhibits prostaglandin synthesis

Therapeutic Effect: Decreased pain and inflammation, reduction of fever

Side Effects: Headache, GI bleeding, hepatitis, constipation, dypepsia, nausea, vomiting, anaphylaxis

Nursing Implications:

- Assess for hypersensitivity reactions
- Assess pain level, ROM
- Monitor temp
- Monitor labs
    - BMP, CBC, LFTs, bleeding time

Drug Card Sample (Side 2)

Nursing Implications (cont):

- •Higher doses ≠ increased effectiveness
- •Ca-administration w/opioids may allow decreased opioid dose
- •Administer 30 min before or 2 hr after meals
  - •May be administered with food, milk, antacids to decrease GI upset
  - •Tablet may be crushed and mixed with fluids/food
- •Patient teaching
  - •Remain upright for 15-30 min after dose, drink full glass of H2O
  - •May cause drowsiness
  - •Avoid alcohol, aspirin, acetaminophen
    - •Alcohol may increase risk of GI bleed
  - •Wear sunscreen
  - •Do not take for greater than 10 days – notify MD
  - •Report skin rashes