Chapter 1

Principles of Pharmacology

Learning Objectives

- Explain the difference between a drug’s generic name and trade name
- Explain concepts of pharmacology, pharmacokinetics, receptor interactions, and pharmacodynamics
- Explain the dose-response relationship

Learning Objectives

- Define enteral and parenteral medications, and identify the routes of administration for each
- Explain first-pass metabolism
- Explain the process of drug metabolism and excretion
Learning Objectives

- Define passive diffusion, carrier-mediated facilitated diffusion, active transport, and passive transport
- Explain the difference and relationship between an agonist drug and antagonist drug

Learning Objectives

- Explain the role of the autonomic nervous system and alpha₁, alpha₂, beta₁, and beta₂ receptors
- Discuss medications used to stimulate the adrenergic receptors: epinephrine, norepinephrine, dopamine, dobutamine, and phenylephrine

Learning Objectives

- Discuss medications used to block the adrenergic receptors: atropine sulfate and scopolamine
Introduction

- Potential causes of level of consciousness
  - Cardiac arrhythmia
  - Diabetic emergency
  - Seizure
  - Toxic ingestion or overdose
  - Stroke
  - Traumatic brain injury

Introduction

- Treatment priorities are the same for all patients.
  - Scene safety
  - Airway
  - Breathing
  - Circulation

Introduction

- Pharmacology can be challenging to master.
  - All drugs have:
    - Specific actions
    - Indications
    - Dosages
    - Adverse effects
Drug Names

- All drugs have at least two names.
  - **Generic**
    - Registered with Food and Drug Administration (FDA)
    - Listed in United States Pharmacopeia-National Formulary (USP-NF)
    - Written in lower case
  - **Trade**
    - Created by pharmaceutical companies
    - When a pharmaceutical company discovers a new drug, scientists assign it a chemical name
    - Manufacturer proposes a generic name to FDA for approval
    - Company then creates a memorable and descriptive trade name
    - Always begin with a capital letter

General Principles

- When approaching pharmacology in general terms, consider:
  - How drug gets into the body
  - How drug moves around the body
  - What tissues drug is able to reach
  - What makes drug work
  - How drug is broken down
  - How drug is removed from the body
**General Principles**

- **Pharmacology**
  - Study of biochemical and physiologic properties of medications

- **Properties of medications include:**
  - Mechanism of action
  - Indications
  - Adverse effects
  - Contraindications
  - Toxicity

**General Principles**

- **Pharmacokinetics**
  - How medication acts
  - How it is absorbed into bloodstream
  - How it is distributed throughout body
  - How the body metabolizes drug
  - How it is eliminated

**General Principles**

- **Receptor interactions**
  - Sites of various tissues to which some drugs bind to exert their physiologic effects

- **Pharmacodynamics**
  - Explains how drug works and interacts with various receptors, other drugs, and enzyme systems within body
General Principles

• Absorption
  ➢ Movement of medication from point of administration into bloodstream for movement throughout body
  ➢ Factors that affect absorption:
    * Dosage
    * Route of administration

General Principles

• Medication dosage
  ➢ Dose
    * Amount of medication administered
  ➢ Dosage
    * Size, frequency, and number of doses to be administered

General Principles

• Medication dosage
  ➢ Dose-response relationship/dose-response curve
    * As dosage increases, so does physiologic effect manifested by drug
    * Effect continues to increase with increasing doses to a point at which the medication no longer produces the desired physiologic effect
General Principles

- Medication form and routes
  - Single medication comes in variety of forms
  - Determined by nature and urgency of medical problem

- Oral
  - Appropriate for stable, chronic conditions
  - Must be swallowed
  - Travel to the stomach
  - Broken down
  - Absorbed in intestine
  - Passed through bloodstream
  - Delivered to site of action
General Principles

- Medication form and routes
  - Enteral
    - Absorbed through GI tract
    - Given orally or rectally
    - Must first pass through liver before being distributed throughout body
    - First pass metabolism
      - Drug is partially metabolized
      - Reduces amount of medication available
  - Variable rate of absorption
  - Potential irritation of mucous lining of the stomach or intestine
  - Possible patient noncompliance
  - Most common and safest route
  - Slow absorption prevents rapid and high blood levels that lead to adverse effects
  - Convenient, without need for sterile technique

- Parenteral
  - Bypass GI tract
  - Injectable medications – directly into muscle, vein, or subcutaneous tissue
  - Rapidly available and circulate throughout body in minutes
  - Requires special training and/or special equipment
  - IV is preferred route for cardiac medications in ALS situations
**General Principles**

- **Medication form and routes**
  - **Loading dose**
    - Rapid therapeutic concentration of drugs in life-threatening emergency
    - Factors that determine dose:
      - Desired serum concentration
      - Volume of distribution
    - Administered via IV to achieve rapid 100% bioavailability
  - **Bioavailability**
    - Percentage of administered drug available in bloodstream to act at target tissue
    - Dose administered minus amount not absorbed by intestine and amount not metabolized by the liver
- **Maintenance dose**
  - Maintains an average concentration of drug at serum-steady states
  - In absence of loading dose, 5 half-lives must pass to achieve steady state of drug concentration
  - **Half-life**
    - Time required for concentration of medication in bloodstream to decrease to half its original level
General Principles

- Medication form and routes
  - Duration of action:
    - Amount of time a single dose produces desired effect
  - Inhaled medications:
    - Used to deliver medication for asthma
    - Are rapidly active, easy to administer, convenient
    - Immediately act on lungs and absorbed into bloodstream
    - Can be given in liquid form

- Liquid medications:
  - Nebulized

General Principles

- Medication form and routes
  - Buccal administration:
    - Administered between cheeks and gums
    - Rapidly absorbed
    - Most common: glucose gel
  - Sublingual administration:
    - Placed under patient’s tongue
    - Rapidly absorbed through oral mucous membranes
    - Most common: nitroglycerin
General Principles

- Medication form and routes
  - Transdermal administration
    - Across the skin
  - Gas
    - Inhaled
    - Most common – O₂
    - Nitrous oxide

Drug Metabolism and Excretion

- Breakdown and change of drug by various chemical reactions throughout body

- Biotransformation
  - Medications are broken down by the liver into active or inactive compound

Drug Metabolism and Excretion

- When drug is absorbed by GI tract, must first go to liver and be acted on by liver enzymes
  - Sites of drug metabolism
    - Liver
    - Kidneys
    - Lungs
**Drug Metabolism and Excretion**

- **Metabolism**
  - Often changes chemical nature of medication, making it inactive
  - Can change effectiveness of medication
  - Patients in whom drug metabolism is increased often require higher dosing
  - Slowed metabolic rate results in a decrease in the breakdown

- **Factors that alter drug metabolism:**
  - Patient age
  - Route of administration
  - Dosage
  - Genetic predisposition of patient
  - Diet or starvation
  - Preexisting disease
  - First-pass metabolism for drug given orally requires significantly higher dose than if given by parenteral route

- **Drug excretion**
  - Removal of drug or metabolite from body
  - Kidney is typically the organ responsible for removal
  - Liver does so less frequently
Pharmacokinetics

- Study of drug absorption, distribution, and excretion
- Absorption determines how rapidly medication becomes available for therapeutic effect
  - More quickly absorbed = more quickly it will assist patient
  - Occurs from any site at which medication is administered

Pharmacokinetics

- First-order kinetics
  - Occurs for all routes, except for IV
  - Constant fraction of medication is absorbed into bloodstream
- Zero-order kinetics
  - Absorption is not delayed
  - Administered directly into bloodstream
  - 100% of medication is available in a brief period

Pharmacokinetics

- Drug distribution
  - Transportation of drug through bloodstream to various tissues and target site
  - Factors that determine how rapidly and to what magnitude medication can accumulate in tissue:
    * Organs that have rich blood supplies receive drug rapidly
    * Lipid or fat-soluble drugs easily cross membranes that separate body compartments
    * Lipid insoluble drugs take longer to cross body compartments
Pharmacokinetics

- Drug distribution
  - Volume of distribution
    - Space that drug would occupy
    - Drug with a high volume of distribution
      - Is fat soluble
      - Can easily pass through membranes into body compartments

Pharmacokinetics

- Drug distribution
  - Bioavailability
    - Fraction of drug that reaches circulation
    - Factors that alter bioavailability:
      - How rapidly medication breaks down and is absorbed in intestinal tract
      - Dietary habits of patient
      - Size of tablet
      - Formulation of medication

Pharmacokinetics

- Drug distribution
  - How medication is absorbed through intestinal tract depends on physical and chemical properties of drug
Pharmacokinetics

- Drug distribution
  - Passive diffusion
    - Occurs when medications penetrate cells by diffusing through cells' membranes
    - Factors for passive diffusion:
      - Chemical nature of drug
      - Chemical charge, fat or water solubility, concentration of drug within body

- Drug distribution
  - Carrier-mediated facilitated diffusion
    - Transportation of drug into a particular cell depends on a second molecule to carry the drug molecule into the cell
    - Administered drug accumulates outside cell membrane
    - Drug binds with carrier macromolecule
    - Carrier molecule then transports bound medication to its destination inside cell

- Drug distribution
  - Carrier-mediated facilitated diffusion
    - Once inside cell, the bound drug dissociates from carrier molecule
    - Drug molecules go to their target site to produce desired effect
    - A saturable process
      - External concentrations do not increase rate of influx
Pharmacokinetics

- Drug distribution
  - Active transport
    * Requires macromolecule to assist in transport
    * Capable of reaching point of saturation
    * Molecules that transport drugs require energy

- Drug distribution
  - Passive transport
    * Occurs when drug molecule moves down concentration gradient
    * Drug moves from area of high concentration to area of low concentration
    * Factors that determine to what degree and how rapidly drug moves into passive transport:
      * Size of drug molecule
      * How easily drug dissolves in water or fat
      * Concentration of drug in body compartments

- Endocytosis
  - Minor method of drug movement
  - Cell forms sac around drug molecule with cell membrane
  - Cell membrane folds inward, taking drug into the cell

- Onset of action
  - Time interval from administration to desired effect
Pharmacokinetics

- **Therapeutic index (TI)**
  - Measurement of the relative safety of drug
  - Factors used to determine:
    - Effective dose 50 (ED\textsubscript{50})
    - Lethal dose 50 (LD\textsubscript{50})
  - Calculated as follows:
    - $TI = \frac{LD_{50}}{ED_{50}}$

Pharmacodynamics

- Explains how drugs work

- **Mechanism of action**
  - Way drug works at target tissue
  - Drug/receptor interactions
  - Drug/enzyme interactions
  - Nonspecific drug interactions

Pharmacodynamics

- **Drug/receptor interactions**
  - Drugs have complex shapes
  - Drugs bind to a receptor
  - Combined drug/receptor interaction then allows drug to act on target tissue
  - Reversible binding
    - Occurs when drug is able to separate from cell’s receptor
    - When drug is removed from receptor, effect of drug stops
  - Irreversible binding
    - Some medications are unable to separate from receptor after they bind to receptor
Pharmacodynamics

- Drug/receptor interactions
  - Agonist
    - Drug that produces desired physiologic effect upon binding with receptor
    - Turn things on
  - Antagonist
    - Drug that diminishes or eradicates physiologic effect of agonist
    - Turn things off

Pharmacodynamics

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- Pharmacologic antagonism
  - Occurs when antagonist binds to receptor and prevents biologic effect of agonist
  - Competitive antagonists
    - Can bind to the receptor in a reversible fashion
  - Noncompetitive antagonists
    - Irreversibly binds to the receptor
**Pharmacodynamics**

- **Drug/receptor interactions**
  - **Attraction**
    - Drugs and receptors have some degree of chemical attraction toward one another
  - **Efficacy**
    - Ability of drug to produce desired biologic effect by binding to and unlocking a given receptor

- **Pharmacodynamics**

  - **Drug/receptor interactions**
    - **Potency**
      - Term used to compare different doses of 2 medications in producing same effect
      - Is independent of that medication's efficacy
    - **Summation**
      - Occurs when 2 medications with same effect given together produce effect in equal magnitude to effects of 2 drugs given independently

- **Pharmacodynamics**

  - **Drug/receptor interactions**
    - **Synergism**
      - Observed effect of 2 medications when given concurrently is greater than effects of medications when given individually
      - Combined effect greater than effect of drug A + effect of drug B
    - **Potentiation**
      - Final enhancement of drug's effect
      - Occurs when drug lacking effect of its own increases effect of second drug
**Pharmacodynamics**

- Drug/enzyme interactions
  - Enzymes
    - Chemicals or compounds that control various chemical changes and reactions within the body
  - Drugs interact with enzymes and increase/decrease enzyme’s mediated chemical reaction
  - Drugs are capable of binding/interacting with various enzymes
    - Either accelerate or arrest their actions

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**Pharmacodynamics**

- Drug/enzyme interactions
  - Enzyme works by binding to starting compound (substrate)
  - Some drugs that act on enzyme systems work by:
    - Mimicking substrate molecule
    - Binding with enzyme system
    - Clogging chemical reaction regulated by that particular enzyme
  - Other drugs can bind enzymes and accelerate a chemical reaction

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**Pharmacodynamics**

- Nonspecific drug interactions
  - Occur when drug acts on target organ/tissue in a method that does not require binding of drug with receptor or enzyme
  - Directly acts on cell or cell’s membrane
Drug Actions and Effects

- Often produce side effects
  - Benign annoyances
    - Headaches
    - Nausea
    - Drowsiness
  - Often treated by reducing dosage or eliminating offending medication

Drug Actions and Effects

- Adverse effects
  - Considered serious
  - Renal failure
  - Bleeding
  - Bone marrow suppression
  - Progression of heart disease

- Idiosyncratic response
  - Rare and unpredicted response to medication

Drug Actions and Effects

- Allergic response
  - Occurs when patient mounts antibody response to a medication to which he or she has been previously sensitized
  - When reexposed to medication, responds with signs/symptoms such as:
    - Rash
    - Itching
    - Swelling
Drug Actions and Effects

- Anaphylactic reaction
  - Allergic reaction with life-threatening manifestations
  - Signs/symptoms:
    - Swelling of airway
    - Inability to breathe
    - Hypotension
    - Shock

- Drug interaction
  - Occurs when effects of 1 drug are modified by or interfere with effects of second drug administered concurrently
  - Result: the effect of 1 drug is increased by the second
  - Two types occur:
    - Those that alter plasma levels of particular medication
    - Those that alter effects of medication

- Drug interaction
  - Many drugs are metabolized by liver enzyme cytochrome P450
    - Theophylline
    - Warfarin
    - Cimetidine
    - Antidepressants
Drug Actions and Effects

- Drug interaction
  - Drugs are able to interact with food and alcohol
    - Via the cytochrome P450 system and competition with the drug’s binding site
    - Most common: monoamine oxidase inhibitors

Large element of drug therapy is manipulation of physiologic functions:
- Heart rate
- BP
- Respiratory effort
- Bowel functions

Autonomic Nervous System (ANS)
- Controls and integrates many major body functions

- Somatic nervous system
  - Controls skeletal muscles and movement

- Provides involuntary control of internal body functions
Autonomic Nervous System

- 2 divisions:
  - Sympathetic
  - Parasympathetic

- Both divisions innervate the:
  - Heart
  - Bronchial smooth muscle
  - Iris of the eye
  - Salivary glands
  - Urinary bladder

Autonomic Nervous System

- Sympathetic nervous system
  - Also innervates vascular smooth muscle, sweat glands, and adrenal medulla
  - Readies body to handle stress
  - Fight-or-flight response
  - Medications that exert effects on the sympathetic nervous system use adrenergic receptors (adrenergic agonists)
Autonomic Nervous System

- Parasympathetic nervous system
  - Responsible for routine housekeeping chores of body
    - Slow heart rate
    - Produce acid for the stomach
    - Empty bladder and bowels
  - Drugs that act on parasympathetic nervous system are called cholinergic agonists

- Adrenergic receptors and activating drugs
  - Are commonly manipulated by medications
  - Adrenaline/epinephrine
    - Increases heart rate
    - Increases heart contractility
    - Increases BP
    - Dilates bronchioles of lungs
    - Net result is to ready the individual for fight-or-flight response
  - Regulates effects through adrenergic receptors:
    - Alpha1
      - Primarily located on peripheral blood vessels
      - Stimulation results in vasoconstriction and elevation of systemic BPs
    - Alpha2
      - Located on nerve endings
      - Provide negative feedback to nerves in sympathetic nervous system
      - Signals process when goal or target is reached
Autonomic Nervous System

- Adrenergic receptors and activating drugs
  - Blood vessels
    - Tone of the vascular smooth muscle is under control of adrenergic receptors
    - Vascular smooth muscles contract and decrease diameter of blood vessels
Autonomic Nervous System

1. Adrenergic receptors and activating drugs
   - Heart
     * Beta agonists are capable of mediating their effect on the heart through the beta, receptor
     * When a cardiac beta receptor is stimulated by a beta agonist:
       ‣ Increased heart rate
       ‣ Increased cardiac output

2. Adrenergic receptors and activating drugs
   - Eyes
     * Muscles of the eye responsible for pupil dilation are stimulated by alpha agonists
     * Drugs that act on both alpha and beta receptors alter pressure inside eye
   - Respiratory tract
     * Stimulation of beta_2 receptors of bronchial smooth muscles results in relaxation of muscles and dilation of the airway
     * Inhaled bronchodilators stimulate beta_2 receptors

3. Drugs that stimulate adrenergic receptors
   - Adrenergic receptors must mimic shape and structure of native agonists of adrenergic receptors
   - Sympathomimetic drugs
     * Mimic actions of sympathetic nervous system
Autonomic Nervous System

- Drugs that stimulate adrenergic receptors
  - In body's natural production of sympathomimetic hormones:
    - Dopamine is precursor to norepinephrine
    - Norepinephrine is precursor to epinephrine
    - Precursor: substance or drug that precedes another substance in development of substance or drug

- When body makes epinephrine, molecule goes through series of modifications before becoming epinephrine
  - Dopamine
    - Primarily stimulates beta_1 receptors of the heart
    - Causes release of norepinephrine from the ANS
    - Can increase heart rate and cardiac output
    - As dopamine is increased, stimulates alpha receptors
    - At higher doses, acts like an epinephrine infusion

- Norepinephrine
  - Similar to epinephrine in its action on beta_1
  - Has less potency on alpha receptors
  - No action on beta_2 receptors
Autonomic Nervous System

- Drugs that stimulate adrenergic receptors
  - Dobutamine
    - Synthetic sympathomimetic drug
    - Adrenergic agent, inotropic
    - Stimulates beta_1 receptors
    - Used to improve cardiac performance in patients with CHF

Autonomic Nervous System

- Drugs that stimulate adrenergic receptors
  - Phenylephrine
    - Pure alpha agonist capable of increasing BP
    - Used as vasopressor in conditions such as septic shock

Autonomic Nervous System

- Drugs that stimulate adrenergic receptors
  - Epinephrine (EpiPen)
    - Binds both alpha and beta receptors
    - Effects on heart are mediated primarily by beta receptors
    - Results in increases in:
      - BP
      - Heart rate
      - Cardiac contractility
      - Cardiac output
    - Can cause cardiac arrhythmias
    - Alpha stimulation causes vasoconstriction and elevation of BP
Autonomic Nervous System

- Drugs that block adrenergic receptors
  - Stimulation of adrenergic receptors influences physiologic responses in different organ systems
  - Beta blockers prevent naturally occurring beta agonists from stimulating the receptor
  - Nonselective beta blockers
  - Selective beta blockers
  - Have both negative chronotropic and inotropic effects

Autonomic Nervous System

- Drugs that block adrenergic receptors
  - Chronotropic drugs affect heart rate
  - Inotropic drugs affect magnitude of the squeeze of heart muscle
  - Reduction of heart rate and inotropy are useful with cardiac disease
  - Conserves O₂ for patients with heart disease
  - Blockage of β₂ receptors results in bronchoconstriction in patients with asthma

Autonomic Nervous System

- Drugs that block adrenergic receptors
  - Propranolol
    - Nonselective beta blocker
    - Can decrease heart rate and cardiac output
  - Beta₁ selective blockers
    - Reduce heart rate and O₂ consumption without adversely affecting lung function
    - Metoprolol
    - Atenolol
Autonomic Nervous System

- Cholinergic receptors and activating drugs
  - Cholinergic receptors
    - Receptors of parasympathetic nervous system
  - Acetylcholine
    - Neurotransmitter used by parasympathetic nervous system
    - Acts on various organs of the body
    - Used in sympathetic nervous system to relay messages, not as neurotransmitter

Autonomic Nervous System

- Cholinergic receptors and activating drugs
  - Types
    - Nicotinic receptors are found in:
      - CNS
      - Autonomic ganglia
      - Striated muscle
    - Muscarinic receptors are found on:
      - Cardiac and smooth muscle
      - Exocrine glands
      - Brain

Autonomic Nervous System

- Cholinergic receptors and activating drugs
  - Atropine
    - Competes with acetylcholine to bind muscarinic receptors
    - Commonly used for bradycardia
    - Dosage guidelines must be strictly followed
    - In high enough dosages, exerts effects on the pulmonary system
    - Drug of choice in nerve agent and organophosphate poisoning
Autonomic Nervous System

- Cholinergic receptors and activating drugs
  - Scopolamine
    - Competitively binds with muscarinic receptor
    - Does not have as potent effect on the heart and lungs as atropine
    - Commonly used for treatment of motion sickness

Questions?