Pharmacology

Definition:
The study of medicine

Important Concepts:
- Pharmacodynamics
- Pharmacokinetics
- Drug effects:
  - Therapeutic and adverse
  - Factors influencing drug effects

Landmarks in Pharmacology
- Foxglove → Digitalis
- Smallpox vaccine by Jenner
- Opium → Morphine
- Penicillin
- Receptors
- Recombinant technology
- Gene therapy
- Pharmacogenetics
- Chronopharmacology

Drug Names
- Chemical: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one
- Generic: diazepam
- Trade/brand: Valium

Pharmacodynamics
- Mechanisms of drug action
- Selective effects on some cells
- Drugs have different mechanisms of action
Mechanisms of Action

Drug-receptor interactions

Non-receptor-mediated actions

Pharmacodynamics

Drug-Receptor Interactions
- Receptors: drugs bind
- Drug must fit receptor (lock and key concept)
- Result: change in cell function

Drug-Receptor Interactions
- Drugs are not perfectly specific
- Receptors are not perfectly specific

Different Drugs, Same Effect
...therefore drug classes and competition in the market

Same Drug, Different Effects
...therefore adverse effects
Potency and Efficacy
- **Potency**: \textit{amount} needed to produce a response
- **Efficacy**: \textit{ability} of drug to produce a response

Dose-Response Curves
- Research use
- Dose determination
- Comparison of drugs

Dose-Response Curves: Key Information
- **Threshold**: minimally effective dose
- **Peak effect**: maximum effectiveness
Compare pain drugs
Example:
- A. Fentanyl 100 mcg (efficacious and very potent)
- B. Morphine 10 mg (efficacious and moderately potent)
- C. Acetaminophen 1000 mg (less efficacious and less potent)

Dose-Response Curves:
Key Information
- Threshold: minimally effective dose
- Peak effect: maximum effectiveness

Agonism vs. Antagonism
- Agonist: binds receptor, activates cell
- Antagonist: binds receptor, blocks receptor

Non-receptor Mediated Drug Effects
- Physical
- Chemical
- Metabolic pathways
Pharmacokinetics

Study of what happens to a drug after administration

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion/elimination

Key Terms

- Onset of action
- Peak effect
- Duration of action

Drug Absorption:
Factors That Affect

- Method of administration
- Solubility
- pH
- Characteristics of GI tract
Administration
- Oral
- Sublingual, buccal
- Rectal
- Topical
  - Skin
  - Inhaled
- Parenteral
  - Subcutaneous
  - Intramuscular
  - Intravenous
  - Epidural
  - Intrathecal

Drug Absorption: Factors That Affect
- Method of administration
- Solubility
- pH
- Characteristics of GI tract

Drug Absorption: Solubility
- Lipid soluble (non-ionized)
- Water soluble (ionized)
- pH determines mix of ionized and non-ionized molecules

Drug Absorption: Factors That Affect
- Method of administration
- Solubility
- pH
- Characteristics of GI tract

Effect of pH
An acid drug in an acid environment is largely non-ionized and thus absorbs easily.

Blood: pH 7.4

After absorption, the pH is higher and the drug becomes ionized preventing diffusion back into the stomach.

Drug Absorption: Factors That Affect
- Method of administration
- Solubility
- pH
- Characteristics of GI tract
Drug Absorption:
GI Tract
- Food or other drugs
- Motility
- Blood flow
- pH and enzymes

Pharmacokinetics
- Absorption
- Distribution
- Metabolism
- Excretion/elimination

Distribution
- Blood flow
- Binding to plasma proteins
- Tissue affinity
- Barriers to penetration

Distribution: Blood flow

Poorly perfused tissue

Distribution
- Blood flow
- Binding to plasma proteins
- Tissue affinity
- Barriers to penetration
**Distribution:**

**Plasma Protein Binding**

*Free (not bound) is the active form*

Drug Alone  Drug Alone

**Distribution:**

**Plasma Protein Binding**

*Competition displaces - increasing active form*

Drugs Together

**Distribution:**

**Blood flow**

**Binding to plasma proteins**

**Tissue affinity**

**Barriers to penetration**

**Distribution:**

**Tissue Affinity**

*Bone, teeth: tetracycline*

*Melanin: chloroquine*

*Adipose: anesthetics, benzodiaepines*

*Muscle: digoxin*

**Distribution:**

**Blood flow**

**Binding to plasma proteins**

**Tissue affinity**

**Barriers to penetration**

**Distribution:**

**Barriers to penetration:**

*Blood-Brain, Blood-Placental, Blood-Testicular*
**Pharmacokinetics**
- Absorption
- Distribution
- Metabolism
- Excretion/elimination

**Distribution: Blood-Brain Barrier**
- Apical chamber (blood)
- Basolateral chamber (brain)

**Metabolism**
- Major site: liver
- Transformation: metabolites
- Conversion: water soluble
- Change to an active form

**Liver Metabolism**
- Glucuronide conjugate
- Sulfonate conjugate
- Glucuronyl transferase
- Sulfotransferase

**Factors That Affect Metabolism**
- Amount of “free” drug
- Liver disease
- Competition for enzymes
- Enzyme induction
**Example: First Pass**

Metabolism

Drugs significantly metabolized on first pass need much higher dose when given by mouth. The normal dose of metoprolol is 50 mg given orally, but only 5 mg if given IV.

**Example: Enzymes**

Grapefruit juice inactivates CYP3A, the enzyme that metabolizes atorvastatin (Lipitor).

The antibiotic rifampin induces CYP3A, the enzyme that metabolizes the estrogen in BCP.

**Pharmacokinetics**
- Absorption
- Distribution
- Metabolism
- Excretion/Elimination

**Excretion-Elimination:**
- Kidney
- Lung
- GI tract

**Excretion-Elimination: Kidney**
- Glomerular filtration
- Tubular secretion and reabsorption

**Excretion-Elimination: Kidney**
- Blood flow
- Solubility
- pH and ionization
- An acid drug in acid urine is largely in the non-ionized form so could be reabsorbed in tubule
Elimination:
Renal Study Questions
- A patient with complete renal failure is to receive a drug that is normally eliminated by the kidneys without being metabolized first. How would dialysis effect when you administer the dose?
- A patient takes an overdose of an acidic drug. How can you change the pH of the urine to prevent reabsorption of the drug into the bloodstream from the tubule?

Excretion-
Elimination
- Kidney
- Lung
- GI tract

Drug Safety
- Adverse drug effect: undesired response to a drug
- 300,000 hospitalizations annually because of adverse drug reactions
- To Err is Human report. 7,000 deaths/year from medication errors.
Drug Safety
- 98,000 deaths were estimated annually in US hospitals due to medical injuries.
- 100,000 Lives Campaign
  - Drug safety and use of evidence based practice.
  - 122,300 lives estimated saved in first 18 months.

Types of Adverse Reactions
- Extension of therapeutic effect
- Non-therapeutic
  - Allergy
  - Idiosyncratic
  - Iatrogenic

Adverse Reactions: Extension of Therapeutic Effect
- Drug has desirable effects
- Too much of a good thing is not good
- Predictable
- Examples
  - Low BP after antihypertensive
  - Fungal overgrowth after antibiotics

Adverse Reactions: Not related to therapeutic effect
- Hypersensitivity/Allergy

Adverse Reactions: Idiosyncrasy
- Extreme sensitivity
- Prolonged drug effects
- Resistance to drug
- Unusual responses

Adverse Reactions: Iatrogenic
- Errors by health providers. Examples from the FDA resulting in death:
  - 20 U insulin ordered. The U was read as 0 and 200 units were given.
  - 260 mg Taxol ordered. 260 mg Taxotere dispensed.
  - 10 mg of methotrexate ordered daily for a pt with arthritis. It should have been weekly.
  - A patient's wife mistakenly applied 6 skin patches of pain medication at one time.
Adverse Reactions: Adverse Reactions:
- Non-Therapeutic Tolerance
- Addiction

Strategies to Decrease
Adverse Drug Reactions
Role of Physician or Advanced Practice Nurse
- Prescribe/Furnish Right drug
- Minimally effective dose
- Evaluate patient & family history
- Evaluate interactions
- Patient teaching

Role of the Pharmacist
- Dispense correct drug in correct dose. Substitutions between brands or generic products State and institutions specific.
- Monitor for interactions
- Patient teaching
- Prescriptions of specific drugs-depends on State

Role of the Nurse
- Administer. Right patient, right drug, right dose, right time, right route
- Observe for effects and side effects
- Patient teaching

Role of the Scientist
- Develop drugs with better specificity for receptors
- Develop drugs with longer and shorter duration of action
- Improve genetic testing

Strategy to Decrease
Drug Reactions
Role of the government
- Fund/direct research
- Regulate
- Monitor
- Teach
Drug Safety
- TALLman letters
  - PredniSONE and PrednisoLONE
  - VinBLAStine and VinCRISStine
- Barcode scanning
- Restricted access
- Double check systems
- Drug name approval
- Non-similar packaging
- “Do Not Use” abbreviations

Drug Interactions
- Additive/Potentiating/
  Synergize or antagonize
- ↑ or ↓ bioavailability
- Induce or suppress metabolizing enzymes

Adverse Effects on DNA
- Carcinogenicity
- Mutagenicity
- Teratogenicity

Legal Considerations: Pre-1906
- Pure Food and Drug Act 1906
- Harrison Narcotic Law 1914
- Federal Food, Drug, and Cosmetics Act 1938
- Dietary Supplement Health and Education Act 1994

Legal Considerations
- Federal Laws governing quality, labeling, effectiveness, marketing and safety of drugs... FDA
- State and Institution may refine
- State Practice Acts govern professionals
Legal Considerations
- Examples:
  - Fines for marketing drugs for non-approved uses
  - Warning letters for false advertising on herbs
  - Ephedra off market
  - Federal prosecution for state approved medical marijuana
  - Name change from Levoxine to Levoxyl to avoid confusion with Lanoxin.

Pharmaceutical Research
- Pre-Clinical
  - Test-tube
  - Animal
  - Clinical: Human Subjects

Human Subjects Research
Committees for the Protection of Human Subjects
- Safety
- Consent
- Ethics

Clinical Trials: Human Subjects Research
- Phase I
- Phase II
- Phase III
- Phase IV

Pharmaceutical Research
- Importance of Post-Marketing Studies
- Examples
  - Phen
  - Vioxx
  - Rezulin

Factors Affecting Drug Responses
Biological
- age
- gender
- genetics
- biorhythm
- nutrition
- pathology
- pregnancy

Psychosocial
- economic
- attitudes
- cultural
- self-medication
- adherence
Drug Responses:
Age
- Neonates
  - Prolonged gastric transit time, variable GI pH, thin skin, small mass, 80% water, membranes + barriers more permeable, low plasma protein levels, bilirubin is protein bound and may be displaced causing brain damage, immature liver and kidneys.
- Children
- Elderly

Drug Responses:
Gender
- Usually not clinically significant

Drug Responses:
Genetics
- Variations in pharmacokinetics and dynamics
- Examples:
  - Warfarin dose highly variable. May take weeks or months to adjust dose. A single gene accounts for 25% of the variation. Asian Americans generally have low dose gene type; African Americans generally have high dose gene type; European Americans are in between. Could we test for variations of this gene?

Drug Responses:
Genetics
- Variations in pharmacokinetics and dynamics
- Examples:
  - Children receiving chemotherapy for leukemia are often cured. Many of those not cured have a genetic variation that causes them to metabolize the drug very quickly. If a genetic test could identify these non-responders before therapy begins, could we give them bigger drug doses or drugs that use a different metabolic pathway?
Drug Responses:
Genetics

Variations in pharmacokinetics and dynamics
Examples:
- BP in Caucasians more responsive to β blockers and ACEi than it is in African Americans.

Drug Responses:
Genetics

Variations in pharmacokinetics and dynamics
Examples:
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For more information on personalized medicine: www.fda.gov/cder/genomics

Drug Responses:
Biorhythm

Chronopharmacology
Biological (circadian) rhythms affect how we respond to medications. The goal of chronopharmacology is to maximize drug effectiveness and decrease toxicity by timing the administration and dose accurately.

Drug Responses:
Biorhythm

Examples
- BP usually highest 10 am. Give beta-blockers in the morning.
- Peak gastric acid secretion between 10pm-2am. Give anti-ulcer meds at bedtime.

Drug Responses:
Nutrition

Poor nutrition often associated with low albumin level in blood.
Malnutrition decreases absorptive surfaces in gut.
Specific nutritional substances may be required by a drug. Examples: alendrolate (FOSAMAX) requires Ca++, erythropoetin (EPOGEN) requires iron.
Excess adipose tissue

Drug Responses:
Pathology

- Renal
- Liver
- Gastrointestinal
- Cardiac
Drug Responses: Pregnancy, Lactation

- Placental barrier
- Breast milk

FDA Pregnancy Categories

- A: remote risk
- B: Slightly more risk
- C: Greater risk
- D: Proven risk
- X: Proven risk, don’t use

Drug Responses: Economic

- Generic vs. name brand
- Insurance reimbursement
- USA prices vs. abroad

Drug Responses: Attitudes

- Does the patient believe there are negative health consequences from the disease, that he/she is susceptible to those consequences and that the drug is capable of preventing a negative outcome?
- Sometimes the disease has no symptoms but the drug has side effects.
- What barriers need to be overcome for the patient to accept and adhere to drug therapy?

Drug Responses: Culture, Ethnicity

- Genetic differences
- Beliefs
  - Drugs vs. herbs
  - Trust in provider
- Health habits

Drug Responses: Self Medication
Drug Responses:
Adherence (Compliance)