Pharmacokinetics and Pharmacodynamics

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Role of the Phamacist

- Finding optimal dosing regimens based on patient factors, disease state, and drug properties.
- Available as information resource.
  - Pharmacy x3224
  - Clinical Office
    - Mike Fraundorfer x5380
    - Antimicrobial Stewardship x5381
    - Resource Pharmacist X5296

What is a Drug?

- A substance intended for use in disease in man or animals.
  - Diagnosis
  - Cure
  - Mitigation
  - Treatment
  - Prevention
- What happens when a drug enters the body?

Pharmacokinetics

- The study of the time course of a drug and its metabolites in the body after administration by any route.
- Characteristics of drug determined by (ADME)
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Absorption

- Process of drug movement from administration site to systemic circulation

Drug Absorpion

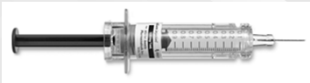
- May be affected by:
  - Manufacturing Process
  - Foods
  - Clinical Condition of the Patient
  - Genetics
  - Dosage form of medication
  - Route of administration

Routes of Administration

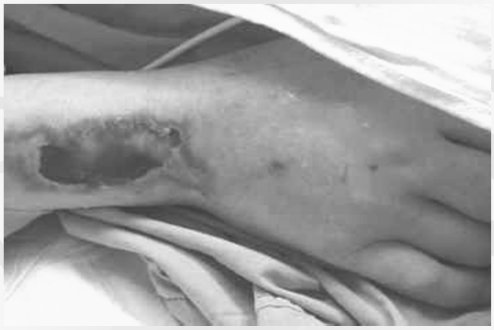
- Parenteral
  - IV, IM, Sub-Q, etc.
- Oral
- Rectal
- Topical
- Transdermal
- Inhalation

Routes of Administration

- Parenteral
  - Usually the quickest form as it reaches the systemic circulation very quickly.
  - Invasive
  - Risks
    - Infection
    - Extravasation



Dopamine Extravasation



Routes of Administration

- Oral
  - Cheaper, easier, and effective
  - Can give systemic or local effect
  - Absorption best in Small Intestine
  - Different dosage forms absorbed at different rates
    - Solutions (fastest)
    - Delayed Release Products (slowest)

Routes of Administration

- Rectal
  - Highly vascular and large surface area
  - Avoids some first-pass metabolism
    - Hepatic metabolism after passing from digestive tract
  - Can give systemic and local effects
  - Can be given as suppositories, enema, or even pill form.

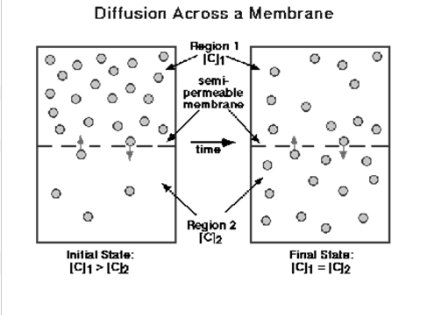
Routes of Administration

- Topical
  - Skin provides barrier to absorption
  - Usually only good for local effects
  - Some systemic uses:
    - Nitroglycerin Ointment

Routes of Administration

- Transdermal
  - Excellent for giving time released medications
  - Releases into body through passive diffusion mechanism
  - Avoids first-pass metabolism
  - Nicotine patch, Fentanyl Patch, Nitroglycerin Patch, etc.

Transdermal Drug Release



Routes of Administration

- Inhalation
  - Highly vascular tissue
  - Mostly local effects (i.e. albuterol)
  - Delivered by
    - Metered Dose Inhaler
    - Dry Powder Inhalation
    - Nebulizer
  - Very dependent on technique

Bioavailability

- Extent of Active Drug Absorption into the patient to reach the site of action
- Parenteral forms assumed to be 100%
- Oral Forms
  - Bioavailabily varies due depending on many factors
- Can effect the peak time and concentration and total concentration (Area Under the Curve)

Distribution

- How the drug becomes available to fluids and tissues
  - Influenced by many factors
    - Perfusion
    - Tissue Binding
    - Regional pH
    - Permeability of cell membranes

Volume of Distribution

- Hypothetical volume of fluid that an amount of drug would need to be uniformly distributed to produce the observed blood concentration.
  - Small: Mostly stays in the circulatory system
  - Large: Accumulates in tissue
- Varies widely from drug to drug.
  - Small: Warfarin, salicylic acid
  - Large: Meperidine, amphetamines

Body fluid/structure	Actual volume (L)
Blood	7
Plasma	4
Whole Body	42

Metabolism

- Chemical alteration of a drug in the body.
  - Metabolites may be active or inactive
    - Accounts for long action of some drugs
  - Pro-Drugs
    - Inactive form given orally and metabolized to active form
      - Lisinopril → Lisinoprilat

How are Drugs Metabolized?

- Goal of Metabolism
  - Increase Hydrophillicity to enhance excretion
- Liver is the major organ for most drug metabolism.
  - Phase I (breakdown or modification)
    - oxidation, reduction, hydrolysis
  - Phase II (binds with compounds in the body)
    - More readily excreted by the kidneys

Phase I Reactions

- Usually mediated by the Cytochrome P450 enzyme system.
  - Found in liver (mostly), lungs, kidneys, and blood plasma
  - Many isolates
    - CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 most common pathways
    - Responsible for some drug interactions
      - 2 drugs may compete for the same enzyme decreasing the metabolism of one of the drugs

Excretion

- How a drug is eliminated from the body without further chemical change.
  - Primarily through the kidneys.
  - Biliary system keeps some drug from being reabsorbed through the GI tract.
  - Excretion through breast milk may harm the baby.

Elimination

- The sum of metabolism and excretion.
- Half-life
  - Time for 50% of drug to be eliminated
  - Important for determining steady state drug levels and dosing regimens.

Pharmacokinetic Factors

- Age and Weight
  - Kidney function decreases with age
  - Hepatic function is not fully developed in infants
  - Increased weight may result in a large volume of distribution

Pharmacokinetic Factors

- Concurrent Illness
  - Renal Dysfunction
    - Mostly determined by creatinine clearance
  - Hepatic Disease
    - Cirrhosis decreases

Pharmacokinetic Factors

- Physiologic Stress
  - Conditions which increase the release of proteins.
    - MI
    - Crohn's Disease
    - Surgery
  - Increases binding of protein bound drugs, decreasing the apparent volume of distribution.

Pharmacokinetic Factors

- Drug Interactions
  - May increase or decrease the metabolism of some drugs.
  - Very difficult to adjust properly

Pharmacokinetic Factors

- Dosing Considerations
  - May effect bioavailability
  - May saturate enzyme pathways required for metabolism
  - May stimulate enzyme pathways required for metabolism

Pharmacodynamics

- Study of biochemical and physiological effects and the mechanism of action of drugs.
- What drug concentration do I need to get a desired effect???

Receptor Theory

- Receptor – protein or macromolocule on a cell membrane in which a drug attaches to produce biochemical changes.
  - Agonist: Drugs that stimulate a response
  - Antagonist: Drugs that block a response

Effects on Receptors

- Non-specific: May hit receptors at different sites
  - Albuterol: Primarily lung, but may also affect the heart
- Non-selective: Hits many different receptors
  - Amitryptyline:
    - Histamine – sedation
    - Alpha receptors – hypotension
    - Cholinergic receptors – dry mouth, blurred vision

1 Drug = 3 Possibilities

- No effect or partial effect
  - Desired effect is not realized
- Therapeutic effect
  - It worked the way we wanted it to!
- Side effects
  - Idiosyncratic:
    - "We didn't see that coming!"
  - Extension of pharmacological effect:
    - "That drug worked *TOO* well!"
    - "Benadryl knocks me out!"

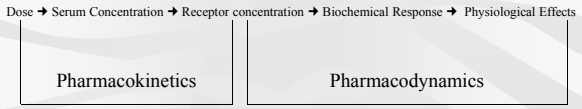
Pharmacodynamic Drug Interactions

- Drug – Drug
  - Increase effect: Sedatives and antihistamines
  - Decrease effect: NSAIDs and diuretics
- Drug – Food
  - Warfarin and green-leafy vegetables
    - Warfarin = Vitamin K blocker
    - Green-Leafy vegetables: High in Vitamin K content

Other Pharmacodynamic Factors

- Age
- Height/Weight
- Gender
- Genetics
- Organ System Function
- Physiological State
- Time of administration

Pharmacokinetic/dynamic Relationship



Tying It All Together

- Aminoglycosides
  - P-kinetics: Used to adjust doses to achieve desired peaks and troughs.
  - P-dynamics: Allows for once daily dosing in some situations based on a peak:MIC ratio
- Cephalosporins
  - Time dependent antibiotic
  - P-Dynamics: Continuous infusion keeps maximum time above MIC