Introduction to Pharmacokinetics

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
Danita Narciso Pharm D
Learning objectives

- Understand compartment models and how they effects drug concentrations
- Understand the two main parameters of pharmacokinetics (Vd and Cl)
- Understand ADME and the characteristics of each
- Know how to estimate how much drug remains after X hours after administrations
- Compare and contrast the 2 phases of metabolism
- Understand how enzyme inhibition and induction work as well as how that affects drugs and prodrugs
- Know the sites of drug excretion/elimination
- Know the key “Plasma level and dose” terms
- Know the parameters of variability in drug action
- Differentiate between an allergy and intolerance
Pharmacokinetics

- What is pharmacokinetics
  - The study of the absorption, distribution, metabolism, and eliminations of drugs with respect to time (ADME)
  - Two main parameters
    - Volume of distribution
    - Clearance
      - 3rd parameter – half life
Volume of distribution (Vd)

- Vd is a theoretical space – measured in liters
  - Average blood volume = 3 liters
  - Vd could be greater than 3 liters, how?
    - 50 mg of drug in your body
    - 5 mg in the blood
    - Vd = 10 L

\[ V_D = \frac{\text{total amount of drug in the body}}{\text{drug blood plasma concentration}} \]
# Volume of distribution (Vd)

## Factors Increasing Vd
- Lipophilic drugs
- Decreased plasma protein binding
- Increased tissue binding

## Factors Decreasing Vd
- Hydrophilic drugs
- Increased plasma protein binding
- Decreased tissue binding
Compartment Models

One compartment models
- Plasma
- Highly perfused organs
  - Liver & kidneys

Two compartment models
- Peripheral tissues
Compartmental models

- IM Injection → Muscle tissue
- Oral drug → GIT
- IV Injection → Central compartment

Absorption:
- Muscle tissue → Central compartment
- GIT → Central compartment

Elimination:
- Elimination in feces
- Elimination of metabolite
- Elimination of parent drug

Distribution:
- Central compartment → Peripheral compartment
Clearance

- Clearance: Portion of the drug removed from the volume of distribution per unit time (L/hr)

- Mechanisms for clearance (can be a combination)
  - Renal elimination
  - Hepatic metabolism
  - Biliary excretion
Clearance – factors that effect

- Rates
  - Absorption rates
    - IV – fast
    - Oral – slow
    - Rectal - sporadic
  - Distribution rates
    - Compartment models – 1 vs. 2
  - Metabolism rates
    - Biotransformation, or metabolites
  - Elimination rates
    - Involves 2 variables: drug concentration and time
    - Elimination rate = -dC/dt
Elimination rates

- Rates of elimination
  - First order
    - The amount of drug removed over time changes
    - The fraction of drug removed remains constant.
    - Concentration dependent
      - Higher concentration = higher rate of removal
      - Lower concentration = lower rate of removal
    - Half-life
      - Amount of time for the drug concentration to decrease by ½ in the volume of distribution
      - 100 mg of drug x was given. Drug x has a half life of 2 hours. In 6 hours how many mgs of drug x would be remaining?
  - Zero order
    - Amount of drug removed per unit time remains the same
    - Fraction of drug removed decreases
    - Concentration independent
    - Concept of half-life does not apply
  - Mixed order
Elimination rates

- **Zero order**
  - Amount of drug removed per unit time remains the same
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  - Concentration independent
  - Concept of half-life does not apply

- **Mixed order**
  - When enzymes play a role in elimination
  - Mixture of first order elimination and zero order
  - First order, enzyme saturation, Zero order
ADME – finally!

- Absorption
- Distribution
- Metabolism
- Excretion
Absorption

- Absorption: Transfer of drug from the site of administration to systemic circulation

- Administration
  - Enteral: Through digestive system
  - Parenteral: Straight into the vasculature
  - Topical: Through the skin, tissues, or membranes

- Accomplished only AFTER drug makes it to systemic circulation
Absorption - Enteral route of administration

- Through the GI tract – tablets, capsules, suspensions, solutions & suppositories
  - Oral
  - Sublingual
  - Rectal

All swallowed medications

Liver

Heart

GI Tract

Sublingual

Rectal
Absorption - Parenteral route of administration

- Directly into systemic circulation – any administration “other than enteral”
  - IV
  - IM
  - IA
  - SC
  - Intrathecal
  - Intrasynovial
  - Intraosseous
  - Intraperitoneal

All parenteral medications

Heart
Liver
GI Tract
Absorption - Topical route of administration

- Directly onto the skin or tissue that is exposed to an area outside the body – liquids, powders, creams, ointments, gels, sprays patches
  - Transdermal
  - Ophthalmic
  - Vaginal
  - Intrauterine
  - Transmucosal – nasal (not orally)
Absorption - Make sure you know....

- Inhalation

- Heart
- Liver
- GI Tract
Absorption - Bioavailability

- Absorption can occur through various routes:
  - Enteral
  - Parenteral
  - Topical

Depends on:
- ROA
- Drug characteristics
- The body
Absorption - Bioavailability

ROA
- First pass metabolism
- Hydrophilicity vs. lipophilicity
- Current GI conditions
  - Food vs. empty stomach
  - pH
  - Enzymes availability
  - GI motility

Drug Characteristics
- Hydrophilicity vs. lipophilicity
- Dosage form
- pKa

The Body
- pH
- Blood flow
- Enzymes
Absorption - First Pass Effect

- Can effect orally administered drugs by up to 90% and more
  - Potency?
- Using a non-oral route and dosage form can help
  - Costly
  - Wrong drug characteristics
- Drug design can help – prodrugs
  - A drug that must undergo first pass metabolism before the active drug compound/molecule is released
Distribution

- Distribution – Relocation of the drug from the systemic circulation to its site of action
  - Movement between compartments
  - Exit the vasculature
Distribution

- Distribution depends on:
  - Size of the drug molecule
  - Lipid solubility
  - Drug pKa and the tissue/blood pH
  - Perfusion to site of action
  - Binding of plasma proteins
Distribution – more on plasma proteins

\[ V_d = \frac{\text{Amount of drug in the body}}{\text{Concentration in the blood}} \]

- Vascular compartment
- Extravascular compartments of the body

\[ V_d = \frac{20}{2} = 10 \]
\[ V_d = \frac{20}{18} = 1.1 \]
\[ V_d = \frac{200}{2} = 100 \]
Distribution – highly protein bound drugs (>90%)

- Drugs > than 90% protein bound
- May be displaced
  - Toxic effects
  - Displacing drug may interfere with clearance
- Reduced number of plasma proteins
  - Toxic effects
Break time
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Metabolism

- Metabolism: The process of chemically inactivating a drug by converting it into a more water-soluble compound or metabolite that can then be excreted from the body.
- Two phases
Metabolism – Phase 1 metabolism

- Make a drug more water soluble by altering the molecule
  - Reactions of
    - Oxidation
    - Hydrolysis
    - Reduction

**LEO says GER:**

- Lose Electrons = Oxidation
  \[ \overset{0}{Na} \rightarrow \overset{+1}{Na} + e^- \]
  Sodium is oxidized

- Gain Electrons = Reduction
  \[ \overset{0}{Cl} + e^- \rightarrow \overset{-1}{Cl} \]
  Chlorine is reduced
Metabolism – Phase 2 (conjugation)

- Make a drug more water soluble by combining it with another molecule
  - Union of a drug with a more water soluble substance
    - Glycine
    - Methyl
    - Alkyl
    - Glucuronide
Metabolism – CYP450

- Metabolism of most lipid soluble drugs
  - Cytochrome P 450 isoenzyme family
    - 3A4
    - 2C9
    - 2C19
    - 2D6
    - 1A2
- Important terms
  - Substrate
  - Inducer
  - Inhibitor
### Metabolism – Enzyme inhibition/induction

<table>
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<tr>
<th>Drug Administered at the same time</th>
<th>Substrate</th>
<th>Inducer</th>
<th>Inhibitor</th>
<th>Drug Concentration</th>
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Patients won’t experience benefit

Patients might experience toxicity

Patients won’t experience benefit

Patients might experience toxicity
# Metabolism – Enzyme inhibitors/inducers

**Major Inhibitors - GPACMAN**
- Grapefruit juice
- Protease inhibitors
- Amiodarone
- Cimetidine
- Macrolide Abx
- Aromatase inhibitors
- Non-dihydropyridine CCBs

**Major Inducers - PSPORCS**
- Phenytoin
- Smoking
- Phenobarbital
- Oxcarbazepine
- Rifampin
- Carbamazepine
- St. John’s Wort
What happens to drug concentrations of drug X if it is a substrate for isoenzyme 2C9 but that particular enzyme is “saturated” (no available enzyme binding sites)?

What is an active metabolite?

What is an inactive metabolite?
Excretion

- Excretion: The process by which drugs are removed from the body.
Excretion - Kidney

- Most important elimination route
- Percent
  - Unchanged
- Free/unbound/water soluble
- pKa and the pH of the urine
  - Weak base drug – excreted in acidic urine
    - Vitamin C
  - Weak acid drug – excreted in alkaline urine
    - Sodium bicarbonate
- Blocking sites of excretion
  - Probenecid to block the tubular excretion of penicillin

Renal Drug Excretion
Excretion - Lungs

- Volatile liquids or gas
- Increased pulmonary blood flow
  - Increase excretion in the lungs
- Decreased pulmonary blood flow
  - Decreased excretion
- Breathalyzer test
Excretion – GI tract

- Biliary excretion
  - Liver, bile, duodenum, to feces

- Enterohepatic recycling
  - Fat soluble substances
Excretion – Sweat/salivary/mammary glands

- Relatively unimportant part of excretion
- Sweat and salivary
  - Tend to cause adverse effects
    - Bad taste
    - Skin reactions
- Mammary glands
  - Drug in breast milk
    - Basic compounds
Plasma level and dose

Terms
- Duration of action
- Half-life
- Minimal effective concentration
- Onset of action
- Peak plasma level
- Steady state
- Termination of action
- Therapeutic range
- Toxic level
Variability in drug action – Average adult dose is based on a drug quantity that produces a certain effect in 50% of the population between age 18-65 and weigh 150 lbs.

- **Age**
  - Children
    - Water & naïve metabolic systems
  - Elderly
    - Less muscle, more fat, & warn out body systems

- **Gender**
  - Women
    - More fat & smaller size
    - Pregnant
  - Men
    - More muscle mass & larger size

- **Genetics**
  - Fast acetylators
  - Non functional enzymes
Drug allergy

- Allergy
  - 2nd exposure
  - Immunes system medicated
  - Anaphylaxis
    - Bronchospasm, hypotension, & death
  - Autoimmune response
    - Thrombocytopenia
    - Anemia
  - Angioedema, arthralgia, & fever
  - Inflammatory reactions
    - Skin rash

- Sensitivity/intolerance
  - Nausea
  - Diarrhea
  - Headache....
Questions