Pharmacokinetics I
Absorption & Distribution

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You do not have to memorize the drugs, their uses, or their pharmacokinetic characteristics for my exam questions.
LEARNING OBJECTIVES

1. Define pharmacokinetics according to the acronym ADME.
2. Discuss the mechanisms (aqueous & lipid diffusion, active transport, etc.) by which drugs are absorbed in the body to reach their sites of action.
3. Describe chemical characteristics of drugs (e.g., solubility, pH) and other factors (e.g., regional differences in blood flow, transporters, non-specific binding) that influence drug absorption.
4. Compare common routes of drug administration, their uses and their limitations.
5. Explain what is meant by a one-compartment and a two-compartment model of drug distribution and how it affects the plasma drug concentration time course.
7. Recognize that differential drug distribution can create drug reservoirs that affect the time course and magnitude of drug effect.

Rational Design of a Therapeutic Regimen

• Dose/formulation
  • Minimum effective concentration
  • Maximum tolerated concentration
• Route of administration & absorption
• First-pass metabolism
• Volume of Distribution
• Clearance
• Area under the curve (AUC)
• Compliance

PHARMACOKINETICS

TIME COURSE OF DRUG ACTION

(as it relates to concentration of drug in the plasma)
PHARMACOKINETICS

• Absorption
• Distribution
• Metabolism
• Excretion  \[
\text{CLEARANCE}
\]

Measurement of Drug Concentration in Plasma

• For most drugs, the concentration of drug at its site of action will be related to the concentration of drug in the systemic circulation.
• Clinical pharmacokinetics relies heavily on measurements of plasma drug concentrations to predict therapeutic and/or toxic effects of drugs.
• Measured plasma drug concentration usually reflects total [drug] in plasma regardless of whether it is bound to proteins or other plasma constituents.

Time Course of Plasma Drug Concentration: Area Under the Curve (AUC)
**Area Under the Curve (AUC)**

**Clinical Significance:**

- Used to compare amount of drug that reaches the systemic circulation by different routes of administration: bioavailability (F).
- Used to compare clearance (CL) of a drug in different individuals after administration of the same dose.

\[
\text{AUC} = \frac{\text{DOSE i.v.}}{\text{CL}} \quad \text{AUC} = \frac{\text{DOSE p.o.}}{\text{CL}(F)}
\]
**DRUG ABSORPTION**

Definition:
The processes by which drugs move from their site of administration to the plasma.

Processes following oral drug administration:
• disintegration of solids and dissolution of drug in fluids of gastrointestinal tract.
• passage of drug across or between cells to reach the systemic circulation.

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**FACTORS AFFECTING DRUG ABSORPTION**

- chemical composition of drug and delivery formulation (tablet, capsule, solvent, etc)
- regional differences in blood flow
- transport mechanisms
- permeability characteristics (lipid solubility)
- ion-trapping
- nonspecific binding
- surface area
I. Passage of drugs across membranes

A. Aqueous diffusion
   - small molecules (<100 kD mol. weight)
   - passive movement driven by concentration gradient
   - route may be paracellular or via aqueous pores

B. Lipid diffusion
   - passive process
   - driven by concentration gradient
   - the rate of absorption increases with increasing drug concentration
   - the more lipid-soluble the faster the rate of transport
   - lipid-soluble drugs cross membranes readily, but may be poorly soluble in aqueous gut fluids, which may limit their absorption.
LIPID SOLUBILITY AFFECTED BY THE DEGREE OF IONIZATION

- Depends on pH of solutions and pKₐ of drug
- *Henderson-Hasselbalch equation:*

<table>
<thead>
<tr>
<th>For Acids</th>
<th>For Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pK_a = \log\left(\frac{[A^+]}{[HA]}\right)$</td>
<td>$pK_a = \log\left(\frac{[B^-]}{[BH^+]}\right)$</td>
</tr>
</tbody>
</table>

Non-ionized form of drug is more lipid-soluble.

Degree of ionization is not linear

ION TRAPPING

Pyrimethamine: $pK_a = 7.0$

- Non-ionized form can diffuse across lipid membranes & so it equilibrates between blood & urine

Total [Drug] in blood = 1.4 μM

Total [Drug] in urine = 11 μM

Katzung BG. Basic & Clinical Pharmacology, McGraw Hill
ACTIVE TRANSPORT

• Requires expenditure of cellular energy.

• Involves specific molecular interactions:
  • transporters for amino acids, glucose, peptides, organic acids/bases etc. can transport structurally related drugs across membranes.
  • The process is saturable.
  • Drugs that are transported by binding to a specific transporter protein can compete with other drugs that utilize the same transporter—this may limit the absorption of either drug.

SURFACE AREA

• Rate of drug absorption across membranes is directly proportional to the available surface area.

• The small intestine is the main site for absorption of most orally administered drugs because it has a much larger surface area than the stomach.

ROUTES OF DRUG ADMINISTRATION

A. Enteral
   1. Oral
   • May accommodate many different physical forms of drug:
     • solutions, suspensions, capsules, tablets, etc.
   • First-pass effect: some drugs are highly metabolized when they pass through the liver—only a fraction (F) of the absorbed drug reaches the systemic circulation (F = bioavailability).
Oral Drug Administration cont'd:

- Enterohepatic circulation: drugs may be secreted into the bile and reabsorbed via the intestine. This can delay delivery to the systemic circulation and may reduce bioavailability.

![](image)

**BIOAVAILABILITY**

The fraction (F) of the administered dose that reaches the systemic circulation in its active form.

A drug may have less than 100% bioavailability if it is incompletely absorbed or if it undergoes metabolism, e.g. while going through the liver via the portal circulation (first-pass metabolism).

\[ F_{oral} = \frac{AUC_{p.o.}}{AUC_{i.v.}} \]

**FIRST-PASS METABOLISM**

- Intestinal
- Hepatic

Oral doses may be higher than intravenous doses because of reduced bioavailability.

\[ Dose_{p.o.} = \frac{Dose_{i.v.}}{F_{oral}} \]
Enteral Drug Administration cont’d:

2a. Sublingual
- Advantages:
  - by-passes portal circulation and therefore avoids first pass metabolism.
  - higher pH may be beneficial for absorption of more basic drugs.
- Disadvantages:
  - taste and/or discomfort

Enteral Drug Administration cont’d:

2b. Buccal
- Similar to sublingual.

“We keep on grinnin` till the weekend comes
Just a pinch between your cheek and gum
All night long, all night long”

“All Night Long” lyrics by The Eagles

3. Rectal
- Advantages:
  - ~50-60% of absorbed drug by-passes portal circulation and therefore avoids first pass metabolism by the liver.
  - useful in cases of nausea and vomiting.
- Disadvantages:
  - discomfort, inconvenience, etc.
B. Pulmonary Drug Delivery

- Absorption is via passive diffusion and is facilitated by a large alveolar surface area.
- Common forms include:
  - volatile gasses
  - aerosol preparations

Local Therapeutic Targeting in the Lungs

- Examples include drugs for asthma or COPD (bronchodilators, anti-inflammatory agents).

Systemic targeting via pulmonary route

- Examples include drugs for migraine (ergotamine) or diabetes (insulin).

Devises for pulmonary drug delivery

- Pressurized metered-dose inhalers
- Dry powder inhalers
- Nebulizers
C. Topical Drug Administration

- Usually for local (non-systemic) therapy.
- Highly lipid-soluble forms of drugs may reach the systemic circulation.
- Common forms include:
  - creams
  - lotions
  - gels
  - ointments
  - shampoos

D. Transdermal Drug Administration

- Passive diffusion of drugs across the skin—driven by concentration gradient.

Transdermal Administration cont’d

- Potential benefits:
  - Controlled release of the drug into the patient—enables a steady blood-level profile
  - User-friendly, convenient, painless, multi-day dosing—improved patient compliance
  - Bypassing the gastrointestinal (GI) tract obviates GI irritation that occurs with some drugs and avoids partial first-pass inactivation by the liver
Transdermal Administration cont’d

• Limitations/risks:
  – skin barrier limits the number of drugs that can be delivered by passive diffusion from an adhesive patch
  – potential discomfort, irritation

SMART INSULIN PATCH RESPONDS TO GLUCOSE LEVELS

E. Parenteral Drug Administration:
Injection of Drugs

• Blood flow:
  – blood flow to the area maintains the concentration gradient.
  – drug absorption is faster in highly vascularized tissues such as skeletal muscle.
### Parenteral Administration cont'd

**Advantages:**
- greater degree of reliability and precision of administered dose
- fewer problems with absorption
  - not affected by food in the stomach
  - no "first-pass effect"

### Parenteral Administration cont'd

**Disadvantages:**
- sight of the needle
- pain
- tissue damage and irritation
- drugs must be in solution
- limited volume

### Parenteral Administration cont'd

**Subcutaneous:**
- **Advantages**
  - slow, even absorption
  - may be used as a depot
  - rate of absorption may be modified by altering blood flow
- **Disadvantages**
  - not effective when peripheral circulation is impaired (e.g. in shock)
  - limited volume
Parenteral Administration cont’d

• **Intramuscular:**
  – Advantages
    • more rapid absorption than subcutaneous
    • rate of absorption may be modified by altering blood flow
  – Disadvantages
    • potential for infection and nerve damage
    • risk of inadvertent i.v. administration

Parenteral Administration cont’d

• **Intravenous:**
  – Advantages
    • Fastest and most reliable means of achieving a defined blood level
  – Disadvantages
    • Risk of overdose by “bolus effect”

**DISTRIBUTION OF ABSORBED DRUG**

• Factors influencing distribution
  • regional differences in blood flow
  • tissue mass
  • transport mechanisms
  • permeability characteristics
    • some membranes resist drug permeation (e.g. BBB)
  • ion-trapping
    • local pH differences can result in relative concentration of drugs in different compartments
  • protein binding
    • plasma proteins can bind a significant fraction of some drugs—only unbound drug distributes to tissues
PROTEIN BINDING

- Many drugs bind to plasma proteins.
  - albumin binds acidic drugs
  - $\alpha_1$ acid glycoprotein binds basic drugs
- Protein-bound drugs are retained in the plasma.

![Diagram of protein binding]

VOLUME OF DISTRIBUTION ($V_d$)

- A measure of how evenly distributed a drug is in the body.
- Following i.v. administration or absorption of a dose of a drug, some of the administered dose stays in the plasma and some distributes to the tissues.
- $V_d$ is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the initial concentration of drug remaining in the plasma.

VOLUME OF DISTRIBUTION

Relates dose (amount) to plasma concentration of drug:

$$V_d = \frac{\text{Dose}}{C_0}$$

$C_0$ = Initial concentration (at time = 0)
The antibiotic tobramycin is given to a patient with gram-negative bacteremia. The patient weight is 60 kg and the patient receives a loading dose of 1.5 mg/kg (90 mg total). If the initial plasma concentration of tobramycin is 6 mg/liter after intravenous dosing, what is the apparent volume of distribution ($V_d$) for this drug?

A) 10 liters  
B) 15 liters  
C) 20 liters  
D) 30 liters  
E) 60 liters

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Theophylline is given to a patient with bronchial asthma in the emergency room. The target plasma level is 10 µg/ml and the patient weighs 50 kg. The average volume of distribution for theophylline is 0.5 liters/kg. Which of the following is the correct loading dose?

A) 100 mg  
B) 250 mg  
C) 500 mg  
D) 1000 mg  
E) 2500 mg

PROTEIN BINDING CAN AFFECT VOLUME OF DISTRIBUTION

90% bound 10% unbound

Vd = 14 L

80% bound 20% unbound

Vd = 24 L

Drug • Protein
Unbound Drug
Protein +
Unbound Drug
Tissue +
Drug • Tissue
DRUG DISTRIBUTION COMPARTMENTS

• The major compartments are:
  — plasma (5% of body weight)
  — interstitial fluid (16%)
  — intracellular fluid (35%)
  — transcellular fluid (2%)
  — fat (20%).

• Lipid-insoluble drugs are mainly confined to plasma and interstitial fluids; most do not enter the brain following acute dosing.

• Lipid-soluble drugs reach all compartments, and may accumulate in fat.

• For drugs that accumulate outside the plasma compartment (e.g. in fat, or by being bound to tissues) $V_d$ may exceed total body volume.

ONE COMPARTMENT VS. TWO-COMPARTMENT DISTRIBUTION

• One-compartment: a rapid equilibrium is achieved between plasma and tissue distribution following drug administration. Plasma concentration-time profile declines mono-exponentially.

• Two-compartment: rapid distribution to a central compartment (plasma) is followed by slow distribution to other tissues/binding sites (second compartment). This results in a bi-exponential plasma concentration-time profile.
TWO-COMPARTMENT MODEL

Drug distribution is not generally uniform.

- Fat and muscle in particular can act as **drug reservoirs**.
  - More drug may be stored in these tissues than remains in the systemic circulation.
  - Gradual release of drug from these sites can prolong the therapeutic effect or result in toxicity.

- Plasma proteins can also serve as a drug reservoir.
  - Sulfonamides may compete for protein binding and increase the unbound fraction of other drugs.
DRUG RESERVOIRS

Additional Reading:

The Merck Manual Online
Robert S. Porter, MD, Editor
Justin L. Kaplan, MD, Senior Assistant Editor

Goodman & Gilman’s Manual of Pharmacology and Therapeutics
Laurence Brunton, PhD, Keith Parker, MD, Editors