PHARMACOKINETICS
WHAT THE BODY DOES TO THE DRUGS

PHARMACODYNAMICS
WHAT THE DRUG DOES TO THE BODY
Pharmacokinetics & Pharmacodynamics

Dosage regimen → Plasma

distribution

elimination

site of action → interaction with receptor → Effect

movement of molecules → cascade to effect
PHARMACOKINETICS
the time course of drug and metabolite concentrations in the body

Pharmacokinetics helps to optimize drug therapy:

• Dose
• Dose regimen
• Dosage form
What happens to a drug after its administration

Absorption
Distribution
Metabolism
Excretion
Mechanisms for drug penetration

(a) Passive diffusion – a passage of (drug) molecules through a membrane that does not actively participate in the process.

(b) Specialized transport mechanisms – a passage of large or lipid insoluble molecules through a membrane, that involves membrane components.
Pharmacokinetic Parameters

- Bioavailability
- Half-life
- Volume of distribution
- Protein Binding
- Clearance
Therapeutic window

Wide therapeutic window:
- Desired effect
- Adverse effect

Narrow therapeutic window:
- Adverse effect
- Desired effect
Therapeutic Window

• Useful range of concentration over which a drug is therapeutically beneficial. Therapeutic window may vary from patient to patient

• Drugs w/ narrow therapeutic windows require smaller & more frequent doses or a different method of administration

• Drugs w/ slow elimination rates may rapidly accumulate to toxic levels….can choose to give one large initial dose, following only with small doses
High-risk pharmacokinetics

risk of serious drug toxicity due to one or more factors:

- narrow therapeutic window
- single metabolic pathway with variable activity
clopidrogel & CYP2C19 polymorphisms & inhibitors (omeprazole)
- single elimination pathway
warfarin & CYP2C9 polymorphism & inhibitors
- very short or very long half-life
- ...
Bioavailability and Bioequivalence

- **Bioavailability** – the rate and extent to which an active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action.

- **Bioequivalence** – the comparison of bioavailability of different formulations, drug products, or batches of the same drug product.
Assessment of Bioavailability

Representative plasma concentration-time relationship after a single oral dose of a hypothetical drug. Area under the plasma concentration-time curve is indicated by shading.
Bioavailability

- **Bioavailability** = the fraction \( F \) of an orally administered drug is calculated by:

\[
F = \frac{\text{(AUC)}_{\text{oral}}}{\text{(AUC)}_{\text{iv}}}
\]

**Factors affecting** \( F \):
- FPE, product formulation, dissolution, chemical and physical interactions with gastrointestinal contents, gastric emptying time, intestinal motility
Bioavailability data are used to determine:

(a) The **amount of drug absorbed** from a formulation or dosage form

(b) The **rate** at which the drug was absorbed

(c) The **duration of the drug’s presence** in the biological fluids or tissue

(d) The **relationship between drug blood levels** and the clinical **efficacy** and **toxicity**
Half-Life $t_{1/2}$.

- the time it takes for a substance to lose half of its pharmacologic, physiologic, or radiologic activity

<table>
<thead>
<tr>
<th>Substance</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amiodarone</strong></td>
<td>26-107 days</td>
</tr>
<tr>
<td><strong>Cisplatin</strong></td>
<td>30 to 100 hours</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>36 to 48 hours</td>
</tr>
<tr>
<td><strong>Fluoxetine</strong></td>
<td>4 to 6 days</td>
</tr>
<tr>
<td><strong>Methadone</strong></td>
<td>15 to 60 hours, in rare cases up to 190 hours.</td>
</tr>
<tr>
<td><strong>Norepinephrine</strong></td>
<td>2 minutes</td>
</tr>
<tr>
<td><strong>Oxaliplatin</strong></td>
<td>14 minutes</td>
</tr>
<tr>
<td><strong>Salbutamol</strong></td>
<td>1.6 hours</td>
</tr>
</tbody>
</table>
Acute vs Steady State

Figure 8–3. Predicted concentration of a drug in plasma and tissue following a rapid intravenous injection. MEC = minimal effective concentration.

Figure 8–5. Accumulation of drug during multiple dosing. It takes four to five half-lives (4–5 $t_{1/2}$) to achieve initial steady state ($C_{PSS}$) on a constant dosage regimen, to achieve a new steady state after an increase in dosage, or to wash out drug from the body after discontinuation. The average steady-state concentration lies somewhere between the peaks and troughs of drug concentration during a dosage interval.
Protein Binding

• Drug distribution into tissues depends on the extent of plasma protein and tissue binding.
• In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly reversibly bound to blood components (eg, plasma proteins, blood cells).
• The most important proteins are albumin, $\alpha_1$-acid glycoprotein, and lipoproteins.
• Unbound drug is available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug occur.
• Saturation of binding sites is the basis of displacement interactions among drugs
**Drug’s protein binding and distribution**

<table>
<thead>
<tr>
<th></th>
<th>Vascular</th>
<th>Extravascular</th>
<th>Intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabic</td>
<td>פלסמה</td>
<td>נוזל חומי-חאדי</td>
<td>נוזל חומי-חאדי</td>
</tr>
<tr>
<td>English</td>
<td>~3 L</td>
<td>~11 L</td>
<td>~28 L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug bound to intravascular proteins</th>
<th>Drug bound to intravascular proteins</th>
<th>Drug bound to intracellular proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>unbound</td>
<td>unbound</td>
<td>unbound</td>
</tr>
</tbody>
</table>
Volume of Distribution

- The apparent volume of distribution is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the concentration in plasma.

\[ V_d = \frac{\text{Amount of drug in body}}{C} \]
Volume of distribution

\[ V = V_P + V_T \cdot \frac{f_{UP}}{f_{UT}} \]

\( V \) reflects ability of the drug to permeate from the plasma to the tissues. The calculation is based on total plasma drug concentrations: bound + unbound.

Low plasma protein binding (high \( f_{UP} \)) → low \( C_o \) (\( C_{u0} + C_{b0} \)) → high \( V \)

Rapid elimination (high \( k \))
General principles of metabolism

\[ \text{drug} \xrightarrow{\text{metabolism}} \text{metabolite} \]

\[ \text{prodrug} \xrightarrow{\text{metabolism}} \text{drug} \]

\[ \text{lipophilic compound} \xrightarrow{\text{metabolism}} \text{hydrophilic compound} \]
Metabolism: pharmacological outcomes

Formation of inactive product

Phenobarbital → hydroxylation → Hydroxyphenobarbital

1. inactive drug (prodrug) to active metabolite
   - Prednisone → reduction → Prednisolone
   - L-dopa → decarboxylation → Dopamine

Formation of active product

2. active drug to active metabolite
   - Procainamide → N-acetylation → N-acetylprocainamide
   - Morphine → glucuronidation → Morphine-6-glucuronide

3. active drug to toxic metabolite
   - Acetaminophen → oxidation → Reactive Metabolite
Examples of drugs that give rise to active metabolites

<table>
<thead>
<tr>
<th>DRUG</th>
<th>METABOLITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetylsalicylic acid</td>
<td>salicylic acid</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>nortriptyline</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>carbamazepine-10,11-epoxide</td>
</tr>
<tr>
<td>codeine</td>
<td>morphine</td>
</tr>
<tr>
<td>diazepam</td>
<td>desmethyldiazepam</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DRUG</th>
<th>METABOLITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>isosorbide dinitrate</td>
<td>isosorbide 5-monoronitate</td>
</tr>
<tr>
<td>morphine</td>
<td>morphine-6-glucuronide</td>
</tr>
<tr>
<td>prednisone</td>
<td>prednisolone</td>
</tr>
<tr>
<td>procainamide</td>
<td>N-acetylpromacainamide</td>
</tr>
<tr>
<td>verapamil</td>
<td>norverapamil</td>
</tr>
</tbody>
</table>
Metabolism classification

Phase I (Functionalization)
- asynthetic
- introduce or expose a functional group increasing polarity
- includes oxidation, reduction and hydrolysis

Phase II (Conjugation)
- synthetic (conjugation reaction)
- couples drug with an endogenous substrate
- conjugation with glucuronic acid, sulfate, acetic acid or amino acid
# Metabolism classification

## Phase I (Functionalization):
- **Oxidation**
  - Cytochrome P450
  - Alcohol dehydrogenase
  - Monoamine oxidase

- **Reduction**
  - Cytochrome P450

- **Hydrolysis**
  - Esterases
  - Amidases

## Phase II (Conjugation):
- Glucuronosyltransferases
- Acetyltransferases
- Sulfotransferases
- Methyltransferases
- Glutathione transferases
- Amino acid transferases
Metabolism of paracetamol (acetaminophen)

- **N-Hydroxylation and rearrangement (CYP-mediated)**
- **Glucuronidation**
- **Sulfation**

- **Toxic reactions with proteins and nucleic acids**
- **Glutathione, cysteine, mercapturic acid conjugates**
Organs that are involved in drug metabolism

- liver
- small intestine
- kidney
- skin
- lungs
- brain
- plasma
- all organs of the body
Factors affecting drug metabolism

- age
- gender
- genetic variation
- state of health
- diet

\{ patient-related \}

- route of drug administration (enteral vs. parenteral)
- degree of protein binding
- substrate competition
- enzyme induction

\{ drug-related \}
Phase I metabolism

- oxidation
- reduction
- hydrolysis

Polar groups are exposed on or introduced to a molecule

\[ R \rightarrow ROH \quad R \rightarrow RCOOH \]

\[ R \rightarrow RSH \quad R \rightarrow RNH_2 \]
Cytochromes P450
Contribution of enzymes to metabolism of marketed drugs

Guengerich, Met Ions Life Sci 2007
Cytochromes P450

- >50% xenobiotics are metabolized in liver via CYP450
- widely distributed throughout body
- enzyme located in endoplasmic reticulum
- frequently referred to as microsomal

contribution of individual enzymes to phase I metabolism

Evans & Relling, Science 1999
Cytochromes P450: CYP3A4

- constitutes ~28% of hepatic Cytochromes P450 content
- is responsible for metabolism of ~60% of all drugs
- can be inhibited or induced by some drugs
- is irreversibly inactivated by bergamottin, component of grapefruit juice

![Graph showing felodipine plasma concentration over time with data points and error bars for different conditions: water, 1 glass of grapefruit juice, 3 days * 5 times grapefruit juice.](image)

*Lown et al., J Clin Invest 1997*
CYP3A4: inhibitors

• Macrolide antibiotics
  – Erythromycin
  – Clarithromycin

• Antifungal agents
  – Ketoconazole
  – Itraconazole

• HIV protease inhibitors

Ketoconazole and terfenadine can produce a drug interaction with fatal consequences!
Cimetidine inhibits CYP450 metabolism of many drugs

CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4

<table>
<thead>
<tr>
<th>Alprazolam</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>
Phase II reactions

- glucuronidation
- glutathione conjugation
- sulfate conjugation
- acetylation
- glycine conjugation
- methylation
- transulfuration
- mercapturic acid synthesis

Evans & Relling, Science 1999
First-pass effect

Gut Lumen

Gut Wall

Portal Vein

Liver

To Site of Measurement

Metabolism

To Feces
Phase II reactions: glutathione conjugation

Glutathione S-transferases (GST)

- cytosolic, mitochondrial, and microsomal proteins
- conjugation of reduced glutathione to a variety of substrates

Non-enzymatic glutathione conjugation

- e.g., to reactive metabolite of paracetamol

![Reduced glutathione (GSH)](image_url)
### Metabolism by intestinal bacteria

<table>
<thead>
<tr>
<th>region</th>
<th>bacteria CFU/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>stomach</td>
<td>$10^3$</td>
</tr>
<tr>
<td>small intestine</td>
<td>$10^4-10^8$</td>
</tr>
<tr>
<td>large intestine</td>
<td>$10^{11}-10^{13}$</td>
</tr>
</tbody>
</table>

**Enzymes:**
- β-glucosidase
- β-glucuronidase
- azo reductase
- nitro reductase
- nitrate reductase
- ...

**Substrates:**
sulfasalazine, chloramphenicol, digoxin, ranitidine, clonazepam, sulindac, omeprazole, metronidazole, isosorbide dinitrate, ...

*Sousa, Int J Pharm 2008*
Renal Elimination
Renal Elimination

- Glomerular filtration: molecules below 20 kDa pass into filtrate. Drug must be free, not protein bound.

- Tubular secretion/reabsorption: Active transport. Drugs with high lipid solubility are reabsorbed passively & therefore slowly excreted.
Serum Creatinine and GFR

• Muscle metabolite - concentration proportional to muscle mass
  – High: muscular young men
  – Low: conditions with muscle wasting
    • elderly
    • muscular dystrophy
    • Anorexia
    • malignancy

• “Normal” range 70 to 140 μmol/litre
Serum Creatinine and GFR

Fraction remaining

Time (half-lives)

N = N_0 * exp(-λt)

Glomerular filtration rate (GFR)
GFR Estimation

- Cockroft-Gault Formula
  \[ \text{CrCl} = F \times (140 - \text{age}) \times \frac{\text{weight}}{\text{Creatinine}} \]
  \[ F_F = 1.04 \]
  \[ F_M = 1.23 \]
  Example
  85 year old Female, 55kg, Creatinine=95
  \[ \text{CrCl} = 33 \text{ml/min} \]

- MDRD Formula
Factors Altering Renal Drug Clearance

- Renal drug clearance is lower [reduce dose] in:
  - Elderly and Newborn
  - Women (20%) than men
  - Kidney and Heart Disease
  - Patients taking secretion blockers (aspirin, probenecid)
Bioequivalence and Generic Drugs
New Drug Development and Approval Process

- **New chemical entity** (e.g., synthesis, isolation).
- **Preclinical studies** - chemistry, physical properties, biological (pharmacology, ADME, toxicology), pre-formulation.
- **Investigational New Drug** Application (IND).
- **Clinical trials** (Phase 1-3) & **preclinical studies** (long term animal toxicology, manufacturing and controls, package and label design).
- **New Drug Application** (NDA).
- **Postmarketing** (Phase 4, adverse reactions, inspection).
## Phases of a Clinical Investigation

<table>
<thead>
<tr>
<th>Clinical testing</th>
<th>Number of subjects</th>
<th>Length</th>
<th>Purpose</th>
<th>Percent of successfully completing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>20-100 (healthy volunteers)</td>
<td>Several months</td>
<td>Mainly safety</td>
<td>67</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Up to several hundred (patients)</td>
<td>Several months to 2 years</td>
<td>Mainly efficacy, but also short-term safety</td>
<td>45</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Several hundred to several thousand (patients)</td>
<td>1-4 years</td>
<td>Safety, efficacy, dosage</td>
<td>5-10</td>
</tr>
</tbody>
</table>
New Drug Development

Preclinical R&D
- Initial synthesis characterization
- Animal testing
  - Short-term
  - Long-term
  - Average 4 Years

Clinical R&D
- Phase 1
- Phase 2
- Phase 3
  - Average 6 Years

NDA Review
- Average 3 Years
- NDA Submitted
- NDA Approved

Post-marketing Surveillance
- Adverse reaction reporting
- Surveys/sampling testing
- Inspections

Average of 12-15 years from initial synthesis to approval of NDA
To gain FDA approval, a generic drug product must have:

- The **same active ingredients** as the ethic drug (inert ingredients may vary).
- Identical **strength**, **dosage form**, and **route** of administration.
- The **same indications** and precautions for use and other labeling instructions.
- **Bioequivalence**.
- The same **batch-to-batch** requirements for **identity**, strength, purity, and quality.
- Manufactured under the same standards of FDA’s **cGMP regulations**, as required for the ethic drug.
Development of a Generic Drug Product

- Characterization of Reference Product
- Design of the Generic Product and Process
- Pivotal Biobatch
- Bioequivalence Study
- Commercial Product Manufacture
Routes of Administration
## Routes of Drug Administration

<table>
<thead>
<tr>
<th>Oral (Per-oral, Per-Os, P.O.)</th>
<th>Intraocular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral (IV, IM, SC)</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Intrarespiratory</td>
</tr>
<tr>
<td>Rectal</td>
<td>Aural - Local only</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Implantable</td>
</tr>
<tr>
<td></td>
<td>Sublingual</td>
</tr>
</tbody>
</table>
The Need for Dosage Form

1. To provide a mechanism of safe and convenient delivery of accurate dosage.
2. To protect the drug substance from the destructive influence of atmospheric oxygen and humidity.
3. To protect the drug substance from the destructive influence of gastric acid after oral administration.
4. To conceal tastes or odor of a drug substance.
5. To provide liquid preparations for insoluble or unstable drugs in the desired vehicle.
6. To provide clear liquid dosage forms of substances.
7. To provide rate-controlled drug release.
8. To provide optimal drug action from topical administration site.
9. To provide for placement of drugs directly in the bloodstream or body tissues.
10. To provide for optimal drug action through inhalation therapy.
Events of Absorption, Metabolism, and Excretion of Drugs after their Administration by Various Routes

- Oral Administration
- Rectal Administration
- Intravenous Injection
- Intramuscular Injection
- Subcutaneous Injection

Gastro-Intestinal Tract

Circulatory System

Tissues

Metabolic Sites

Drug

Excretion

Drug

Metabolites
Factors in Choosing the Route of Administration

- Type of desired effect – local/systemic.
- Physiochemical properties, solid or insoluble.
- Rapidity of effect, oral, intramuscular (IM), intravascular (IV).
- Quality of effect, Magnesium sulphate orally is purgative, but rectally ↓ I/c tension.
- Condition of patient, conscious or unconscious, vomiting.
# Routes of Drug Administration

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Time to onset of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>seconds</td>
</tr>
<tr>
<td>IM, SC, aerosol, gas</td>
<td>minutes</td>
</tr>
<tr>
<td>Tablets, capsules, solutions, suspensions, powders, granules</td>
<td>minutes - hours</td>
</tr>
<tr>
<td>Sustained Release (SR)-tab, Enteric Coated (EC)-tab</td>
<td>hours</td>
</tr>
<tr>
<td>Implants</td>
<td>days</td>
</tr>
</tbody>
</table>
Oral Route of Drug Administration

Advantages:

The most natural, un-complicated convenient, and safe means of administrating drugs.

Disadvantages:

- Slow drug respond (compared with IV administration).
- Chances of irregular absorption of drugs.
- Depends upon the amount and type of food in the gastrointestinal tract (GIT).
- Destruction of certain drugs by the acid reaction of the stomach or by GIT enzymes.
Topical Application - Mucous Membrane

• Conjunctiva, nasopharynx, oropharynx, vagina, urethra, urinary bladder, ear, nose, anal canal for local effects
• Synthetic ADH to nasal mucosa for systemic effects
• Absorption rapid
• Local anesthetic for local effects rapidly absorbed, produce systemic toxicity
• Ointment, cream, drops, jelly, powder, tablet, suppository, pessary.
Topical Application

- Absorption: surface area, lipid solubility.
- Few drugs readily penetrate skin.
- Burned, denuded, abraded, inflamed skin - increase systemic absorption.
- Toxicity by highly lipid soluble insecticides.
- Controlled-release topical.