

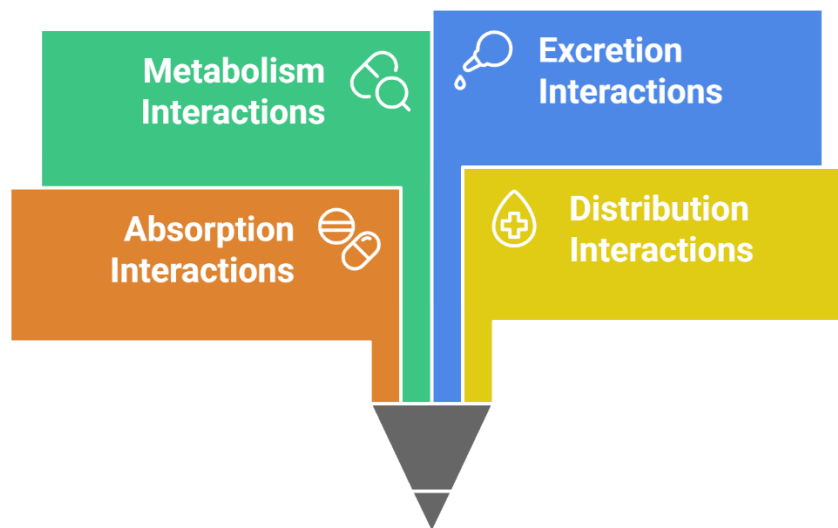
Pharmacokinetics of Drug Interaction

Pharmacokinetic Drug Interactions

Definition:

- Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism, or excretion (ADME) of another drug, thereby modifying its plasma concentration and clinical effects.

Phases of Pharmacokinetics Interactions



1. Absorption Interactions:

- One drug can alter the gastrointestinal (GI) absorption of another.
- **Mechanisms:**
 - Altered gastric pH (e.g., antacids increasing stomach pH affecting drug solubility).
 - Changes in GI motility (e.g., metoclopramide accelerates gastric emptying; opioids slow it).
 - Formation of complexes (e.g., tetracyclines with calcium, iron, or magnesium leading to insoluble chelates).
 - Competition for transporters (e.g., some antivirals compete for intestinal transport proteins like P-gp).
 - Alteration of gut flora (e.g., antibiotics disrupting bacteria that activate or deactivate certain drugs like oral contraceptives).

2. Distribution Interactions:

- Drugs may compete for plasma protein binding sites (e.g., albumin).
- Displacement of one drug from protein-binding sites by another can increase the free (active) concentration of the displaced drug.

- However, this is usually transient due to compensatory redistribution and elimination mechanisms.
- **Example:**
 - Warfarin (highly protein-bound) can be displaced by sulfonamides, increasing free warfarin levels, and leading to bleeding risks.

3. **Metabolism Interactions:**

- These are the **most clinically significant pharmacokinetic interactions**.
- They occur primarily in the **liver**, where drugs are metabolized by **cytochrome P450 (CYP)** enzymes.
- **Drugs can be:**
 - **Inducers:** increase enzyme activity, speeding metabolism.
 - **Inhibitors:** decrease enzyme activity, slowing metabolism.
- **Result:** The levels of the affected drug can either rise (leading to toxicity) or fall (leading to therapeutic failure).

4. **Excretion Interactions:**

- Occur mainly in the **kidneys (renal excretion)** or via **bile (biliary excretion)**.
- **Drugs can:**
 - Compete for active tubular secretion (e.g., probenecid inhibits the renal excretion of penicillin).
 - Alter urinary pH, affecting reabsorption and elimination (e.g., alkalinization of urine increases excretion of acidic drugs).
 - Inhibit biliary transporters, reducing drug clearance (explained in more detail in section c).

Clinical Significance:

- These interactions can lead to:
 - Enhanced drug toxicity
 - Therapeutic failure
 - Need for **dose adjustment** or **monitoring**
- Particularly important for drugs with **narrow therapeutic index** (e.g., warfarin, digoxin, lithium).

Inhibition and Induction of Drug Metabolism

Overview of Drug Metabolism

- Drug metabolism primarily occurs in the **liver** and is divided into two phases:

A. Phase I – Functionalization Reactions:

- Involves **oxidation, reduction, and hydrolysis**, mainly mediated by **Cytochrome P450 (CYP450)** enzymes.

B. Phase II – Conjugation Reactions:

- Includes **glucuronidation, sulfation**, acetylation, methylation, etc., which make drugs more water-soluble for excretion.
- Changes in the activity of these metabolic enzymes due to other drugs can lead to **significant drug interactions**.

Induction vs Inhibition Onset:

• Enzyme Inhibition:

- **Rapid onset:** hours to a few days.
- **Resolution:** quickly after discontinuation of the inhibitor.

• Enzyme Induction:

- **Slow onset:** several days to weeks (due to increased protein synthesis).
- **Prolonged effect:** can persist **after withdrawal** due to enzyme half-life and turnover.

Clinical Relevance of Enzyme Inhibition & Induction:

- Particularly important in drugs with:
 - A **narrow therapeutic index** (e.g., warfarin, digoxin, theophylline)
 - **Long half-lives**
 - **Active metabolites**
- These interactions often require **close monitoring, dose adjustments, or therapeutic alternatives**.

Inhibition of Drug Metabolism/ Enzyme Inhibition

Definition:

- When a drug reduces the metabolic capacity of an enzyme (particularly CYP enzymes), it is known as enzyme inhibition.

Types of Inhibition

1. Competitive Inhibition

- Two drugs compete for the same enzyme active site.
- Reversible and concentration-dependent.

2. Non-Competitive Inhibition

- Inhibitor binds to a different site, changing enzyme shape and function.

3. Mechanism-Based (Suicide) Inhibition

- Inhibitor binds irreversibly to the enzyme.
- e.g., *Erythromycin* irreversibly inhibits **CYP3A4**.

Consequences:

- **Increased plasma concentration** of the drug being metabolized.
- Higher risk of **toxicity**, especially for drugs with a narrow therapeutic index (e.g., theophylline, warfarin, digoxin).

Example CYP Inhibitors:

- **CYP3A4**: ketoconazole, erythromycin, grapefruit juice
- **CYP2D6**: fluoxetine, paroxetine
- **CYP2C9**: amiodarone, fluconazole

Clinical Examples:

- **Statins (simvastatin) + macrolide antibiotics** → increased statin levels → risk of rhabdomyolysis
- **Warfarin + fluconazole** → increased INR → bleeding risk

Key Enzymes Involved:

- Mainly **Cytochrome P450 (CYP)** enzymes:
 - CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2

Induction of Drug Metabolism/ Enzyme Induction

Definition:

- Enzyme induction occurs when a drug **increases the synthesis or activity** of metabolizing enzymes, enhancing the metabolism of co-administered drugs.

Mechanism:

- Many inducers activate nuclear receptors such as:
 - **Pregnane X Receptor (PXR)** and **Constitutive Androstane Receptor (CAR)**.
- These receptors bind to DNA response elements, upregulating the transcription of CYP genes (especially CYP3A4, CYP2C9, CYP2B6).

Consequences:

- Decreased plasma levels of the affected drug.



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