Lecture Notes: Session 8 - Drug Metabolism: Principles of Phase I

SNS College of Pharmacy and Health Sciences

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Introduction

This lecture focuses on Phase I drug metabolism, which involves chemical modifications to drugs to increase their polarity, facilitating excretion or further metabolism. Phase I reactions include oxidation, reduction, and hydrolysis, primarily catalyzed by enzymes such as cytochrome P450 (CYP450). Using diazepam as an example, this session explores these reactions, their mechanisms, and their impact on drug pharmacokinetics.

1 Phase I Drug Metabolism

Phase I metabolism introduces or unmasks functional groups (e.g., -OH, -NH2, -COOH) on drug molecules, typically making them more polar and reactive. These reactions prepare drugs for Phase II conjugation or direct excretion. The primary enzyme family involved is cytochrome P450, located mainly in the liver endoplasmic reticulum.

1.1 Oxidation

Oxidation reactions involve the addition of oxygen or removal of hydrogen, increasing a drug's polarity. They are the most common Phase I reactions, predominantly catalyzed by CYP450 enzymes.

Types of Oxidation Reactions:

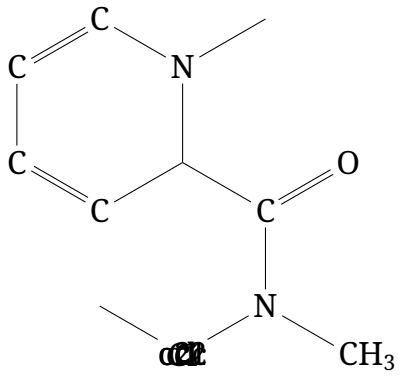
- **Aromatic Hydroxylation:** Addition of a hydroxyl group to an aromatic ring.
- **Aliphatic Hydroxylation:** Hydroxylation of alkyl chains.
- **N-Dealkylation:** Removal of alkyl groups from nitrogen atoms.
- **O-Dealkylation:** Removal of alkyl groups from oxygen atoms.
- **N-Oxidation:** Formation of N-oxides.
- **S-Oxidation:** Formation of sulfoxides or sulfones.
- **Deamination:** Removal of amine groups.

Enzymes:

- **CYP450:** A superfamily of heme-containing monooxygenases (e.g., CYP3A4, CYP2D6) that catalyze oxidation using molecular oxygen and NADPH.
- Other enzymes: Flavin-containing monooxygenases (FMO), monoamine oxidase (MAO).

Example - Diazepam:

- **Chemical Structure:**



- **Metabolism:** Diazepam undergoes N-demethylation (via CYP3A4/CYP2C19) to form desmethyldiazepam, an active metabolite, and hydroxylation to form temazepam.
- **Reaction:**

$$\text{Diazepam} \xrightarrow{\text{CYP3A4}} \text{Desmethyldiazepam} + \text{CH}_3\text{OH}$$

- **Pharmacological Impact:** Desmethyldiazepam has a longer half-life (36–200 hours vs. diazepam's 20–70 hours), contributing to prolonged sedative effects.

1.2 Reduction

Reduction reactions involve the addition of hydrogen or removal of oxygen, less common than oxidation but significant for certain drugs.

Types of Reduction Reactions:

- **Nitro Reduction:** Conversion of nitro groups (-NO_2) to amines (-NH_2).
- **Azo Reduction:** Conversion of azo groups (-N=N-) to amines.
- **Carbonyl Reduction:** Conversion of ketones or aldehydes to alcohols.

Enzymes:

- **CYP450:** Some isoforms catalyze reduction under low oxygen conditions.
- **NADPH-Cytochrome P450 Reductase:** Transfers electrons for reduction.
- **Microbial Enzymes:** Gut microbiota contribute to azo and nitro reductions.

Example - Diazepam:

- While reduction is less common for diazepam, related benzodiazepines (e.g., clonazepam) with nitro groups may undergo nitro reduction to amines, altering activity.
- **Hypothetical Reaction:**

$$\text{Clonazepam (7-NO}_2\text{)} \xrightarrow{\text{Reduction}} \text{7-Aminoclonazepam}$$

- **Pharmacological Impact:** Reduced metabolites may have altered potency or toxicity.

1.3 Hydrolysis

Hydrolysis involves the cleavage of chemical bonds by water addition, often targeting esters, amides, or epoxides.

Types of Hydrolysis Reactions:

- **Ester Hydrolysis:** Conversion of esters to alcohols and carboxylic acids.
- **Amide Hydrolysis:** Conversion of amides to amines and carboxylic acids.
- **Epoxide Hydrolysis:** Conversion of epoxides to diols.

Enzymes:

- **Esterases:** Carboxylesterases, cholinesterases.
- **Amidases:** Cleave amide bonds.
- **Epoxide Hydrolases:** Microsomal and cytosolic forms.

Example - Diazepam:

- Diazepam itself is not typically hydrolyzed, but related esters (e.g., midazolam) undergo ester hydrolysis.
- **Related Example - Aspirin:**

$$\text{c1ccc2c(C(=O)CC(=O)O)c2} \xrightarrow{\text{Esterase}} \text{Salicylic Acid} + \text{CH}_3\text{COOH}$$

- **Pharmacological Impact:** Hydrolysis of aspirin produces salicylic acid, the active anti-inflammatory metabolite, with a longer half-life.

2 Cytochrome P450 Enzymes

CYP450 enzymes are the primary catalysts of Phase I metabolism, responsible for 75

Key Features:

- **Location:** Primarily in liver hepatocytes (endoplasmic reticulum), also in intestines, lungs, and kidneys.

- **Isoforms:** Major isoforms include CYP3A4 (most abundant), CYP2D6, CYP2C9, CYP1A2, and CYP2C19.
- **M**echanism: Catalyze monooxygenation:

$$\text{Drug} + \text{O}_2 + \text{NADPH} + \text{H}^+ \xrightarrow{\text{CYP450}} \text{Drug-OH} + \text{H}_2\text{O} + \text{NADP}^+$$

- **Induction/Inhibition:** Drugs can induce (e.g., rifampin for CYP3A4) or inhibit (e.g., ketoconazole for CYP3A4) these enzymes, affecting metabolism rates.

Example - Diazepam:

- Metabolized by CYP3A4 and CYP2C19, producing desmethyldiazepam and temazepam.
- **Clinical Relevance:** CYP3A4 inducers (e.g., carbamazepine) accelerate diazepam clearance, reducing efficacy, while inhibitors (e.g., grapefruit juice) prolong its effects.

3 Clinical Implications

- **Pharmacokinetics:** Phase I metabolism alters drug half-life, bioavailability, and activity. Active metabolites (e.g., desmethyldiazepam) may prolong therapeutic effects.
- **Drug Interactions:** CYP450 induction or inhibition can lead to toxicity or reduced efficacy (e.g., diazepam with CYP3A4 inhibitors).
- **Toxicity:** Some Phase I metabolites are reactive (e.g., epoxides), requiring Phase II conjugation to detoxify.
- **Design Considerations:** Medicinal chemists design drugs to optimize metabolism (e.g., adding fluorine to block oxidation sites).

4 Key Learning Points

- Phase I metabolism (oxidation, reduction, hydrolysis) increases drug polarity, primarily via CYP450 enzymes.
- Oxidation (e.g., N-demethylation of diazepam) is the most common reaction, catalyzed by CYP3A4 and others.
- Reduction and hydrolysis, though less frequent, are critical for specific drugs (e.g., aspirin hydrolysis).
- Understanding Phase I metabolism guides drug design to optimize efficacy, reduce toxicity, and manage drug interactions.