Lecture Notes: Session 9 - Drug Metabolism: Principles of Phase II

SNS College of Pharmacy and Health Sciences

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Introduction

This lecture focuses on Phase II drug metabolism, which involves conjugation reactions that increase a drug's polarity to facilitate excretion. Phase II reactions include glucuronidation, sulfation, and acetylation, among others, and are critical for detoxifying drugs and their metabolites. Using morphine as an example, this session explores the mechanisms, enzymes, and clinical implications of these processes, emphasizing how increased polarity enhances drug elimination.

1 Phase II Drug Metabolism

Phase II metabolism involves the conjugation of a drug or its Phase I metabolite with an endogenous substrate, producing a more polar, water-soluble compound that is readily excreted in urine or bile. These reactions typically occur in the liver, catalyzed by specific enzymes, and enhance detoxification by reducing pharmacological activity and increasing hydrophilicity.

1.1 Overview of Phase II Reactions

Key Characteristics:

- *Conjugation:* Addition of polar groups (e.g., glucuronic acid, sulfate, acetyl) to drugs or metabolites.
- *Purpose:* Increases molecular weight and polarity, facilitating excretion via kidneys or bile.
- *Enzymes:* Transferases, such as UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and N-acetyltransferases (NATs).
- *Functional Groups Targeted:* Hydroxyl (-OH), amino (-NH2), carboxyl (-COOH), or thiol (-SH) groups introduced or exposed during Phase I.

Clinical Relevance:

- Enhances drug clearance, reducing toxicity and accumulation.

- Conjugates are generally inactive, though some (e.g., morphine-6-glucuronide) retain pharmacological activity.

1.2 Glucuronidation

Definition: Glucuronidation involves the conjugation of a drug or metabolite with glucuronic acid, catalyzed by UDP-glucuronosyltransferases (UGTs) in the liver and intestine.
Mechanism:

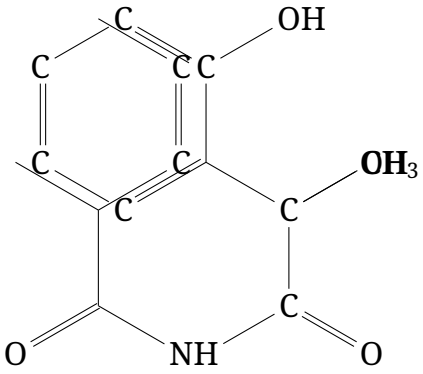
- UDP-glucuronic acid (UDPGA) donates glucuronic acid to a nucleophilic group (e.g., -OH, -COOH) on the drug, forming a β-glucuronide.
- The reaction occurs in the endoplasmic reticulum, requiring UDPGA as a cofactor.

Pharmacological Implications:

- Increases polarity and molecular weight, promoting biliary or renal excretion.
- Example: Morphine-6-glucuronide is pharmacologically active, contributing to analgesia, while morphine-3-glucuronide is inactive.

Example - Morphine:

- **Chemical Structure:** Morphine is a phenanthrene alkaloid with two hydroxyl groups (3-OH and 6-OH).



- **Glucuronidation Reaction:** The 3-OH and 6-OH groups are conjugated with glucuronic acid, forming:
  - Morphine-3-glucuronide (inactive, major metabolite, excreted in urine).
  - Morphine-6-glucuronide (active, potent analgesic, longer half-life than morphine).
- **Pharmacokinetics:** Morphine has a half-life of 2–3 hours, while morphine-6-glucuronide extends analgesia due to its half-life of 4–6 hours.
- **Clinical Relevance:** Glucuronidation enhances morphine's excretion but complicates dosing due to active metabolites.

SAR Notes: The presence of hydroxyl groups is critical for glucuronidation. Structural modifications (e.g., methylation) can reduce conjugation efficiency.

1.3 Sulfation

Definition: Sulfation involves the transfer of a sulfate group from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to a drug or metabolite, catalyzed by sulfotransferases (SULTs) in the cytosol.
Mechanism:

- Targets hydroxyl or amino groups, forming sulfate esters or sulfamates.
- Increases polarity and solubility, facilitating excretion.

Pharmacological Implications:

- Sulfation is a high-affinity but low-capacity pathway, often saturated at high drug doses.
- Sulfated conjugates are typically inactive and excreted in urine.

Example - Acetaminophen:

- **Chemical Structure:** c1cc—NH—C(=O)CH_3—OH
- **Sulfation Reaction:** The phenolic hydroxyl group is conjugated with a sulfate group, forming acetaminophen sulfate.
- **Pharmacokinetics:** Sulfation accounts for 30–40% of acetaminophen metabolism at therapeutic doses, with a half-life of 2–3 hours.
- **Clinical Relevance:** Sulfation reduces acetaminophen's toxicity by diverting it from the toxic NAPQI pathway, but saturation at high doses increases hepatotoxicity risk.

SAR Notes: The phenolic hydroxyl group is essential for sulfation. Electron-withdrawing groups near the hydroxyl can enhance SULT affinity.

1.4 Acetylation

Definition: Acetylation involves the transfer of an acetyl group from acetyl-coenzyme A to a drug or metabolite, catalyzed by N-acetyltransferases (NATs) in the cytosol.
Mechanism:

- Targets primary amines, hydrazines, or hydroxylamines, forming amides or acetates.
- Increases polarity, though less than glucuronidation or sulfation.

Pharmacological Implications:

- Acetylation is genetically variable (e.g., fast vs. slow acetylators), affecting drug clearance and toxicity.
- Often inactivates drugs but can activate prodrugs (e.g., isoniazid).

Example - Isoniazid:

- **Chemical Structure:** c1cc(C(=O)N)NHNH$_2$

- **Acetylation Reaction:** The hydrazine group is acetylated, forming acetylisoniazid, which is further metabolized to acetylhydrazine (potentially hepatotoxic).
- **Pharmacokinetics:** Fast acetylators clear isoniazid more rapidly (half-life 1 hour) than slow acetylators (half-life 3 hours).
- **Clinical Relevance:** Acetylation status influences dosing and toxicity risk in tuberculosis treatment.

SAR Notes: The presence of a primary amine or hydrazine is critical for acetylation. Aromatic rings enhance NAT substrate specificity.

2 Increased Polarity in Phase II Metabolism

Phase II reactions significantly increase a drug's polarity, aiding excretion:

- **Glucuronidation:** Adds a large, polar glucuronic acid (MW 176), increasing water solubility and biliary excretion.
- **Sulfation:** Adds a sulfate group (MW 80), enhancing solubility and renal excretion.
- **Acetylation:** Adds an acetyl group (MW 42), moderately increasing polarity, often combined with other pathways for excretion.

Clinical Impact:

- Reduces drug accumulation, minimizing toxicity.
- Facilitates clearance of both parent drugs and Phase I metabolites.
- Example: Morphine's glucuronides are highly water-soluble, ensuring efficient urinary excretion, though active metabolites complicate pharmacodynamics.

3 Clinical Implications

- **Dosing Adjustments:** Active conjugates (e.g., morphine-6-glucuronide) require consideration in renal impairment.
- **Toxicity Management:** Saturation of sulfation in acetaminophen overdose shifts metabolism to toxic pathways, necessitating antidotes like N-acetylcysteine.
- : Acetylation variability (e.g., isoniazid) affects therapeutic outcomes and side effect profiles.
- Design: Phase II metabolism informs prodrug design (e.g., esters cleaved to active forms) and structural modifications to prolong or shorten half-life.

4 Key Learning Points

- Phase II metabolism (glucuronidation, sulfation, acetylation) increases drug polarity for excretion, catalyzed by transferases (UGTs, SULTs, NATs).
- Glucuronidation (e.g., morphine) produces active or inactive conjugates, impacting pharmacodynamics.
- Sulfation (e.g., acetaminophen) is high-affinity but saturable, influencing toxicity.
- Acetylation (e.g., isoniazid) is genetically variable, affecting clearance and safety.
- Understanding Phase II reactions guides drug design for optimized pharmacokinetics and reduced toxicity.