Lecture Notes: Session 10 - Factors Affecting Drug Metabolism and Course Wrap-Up

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Introduction

This lecture concludes Unit I: Introduction to Medicinal Chemistry by exploring factors affecting drug metabolism, including age, genetics, and stereochemistry, with a focus on enantioselective metabolism. It also includes a comprehensive wrap-up of the unit, summarizing key concepts such as the history of medicinal chemistry, physicochemical properties, and drug metabolism principles. Using warfarin as an example, this session highlights how these factors influence drug pharmacokinetics and therapeutic outcomes.

1 Factors Affecting Drug Metabolism

Drug metabolism involves biochemical processes that transform drugs into more polar, excretable forms via Phase I (e.g., oxidation) and Phase II (e.g., conjugation) reactions. Several factors influence the rate and extent of metabolism, impacting drug efficacy and safety.

1.1 Age

Description: Age affects drug metabolism due to variations in enzyme activity and organ function across life stages.
Pharmacological Implications:

- *Neonates and Infants:* Reduced cytochrome P450 (CYP450) enzyme activity and immature liver function lead to slower metabolism, requiring lower doses to avoid toxicity.
- *Elderly:* Decreased hepatic blood flow, reduced enzyme activity, and lower renal clearance prolong drug half-life, increasing the risk of accumulation.

Example - Warfarin:

- Chemical Structure: c1cc2c CC1C=c3ccOccc3C=ccC1c2
- Warfarin is metabolized by CYP2C9 (S-enantiomer) and CYP1A2 (R-enantiomer). In elderly patients, reduced CYP activity and lower hepatic blood flow increase warfarin's half-life, necessitating dose adjustments to prevent bleeding.

1.2 Genetics

Description: Genetic polymorphisms in drug-metabolizing enzymes (e.g., CYP450 isoforms) lead to inter-individual variability in metabolism.
Pharmacological Implications:

- *Poor Metabolizers (PMs):* Individuals with defective enzyme alleles (e.g., CYP2C9*2/*3) metabolize drugs slowly, increasing drug exposure.
- *Extensive or Ultra-Rapid Metabolizers (EMs/UMs):* Those with normal or enhanced enzyme activity metabolize drugs quickly, potentially reducing efficacy.

Example - Warfarin:

- CYP2C9 polymorphisms (e.g., CYP2C9*3) reduce metabolism of (S)-warfarin, the more potent enantiomer, leading to increased anticoagulant effects and bleeding risk.
- Pharmacogenomic testing guides dosing to account for genetic variations.

1.3 Stereochemistry (Enantioselective Metabolism)

Description: Stereochemistry, particularly chirality, influences metabolism as enzymes may preferentially metabolize one enantiomer over another.
Pharmacological Implications:

- Enantiomers of a chiral drug may have different metabolic pathways, clearance rates, or pharmacological activities.
- Stereoselective metabolism can lead to accumulation of one enantiomer, altering therapeutic outcomes.

Example - Warfarin:

- Warfarin exists as (R)- and (S)-enantiomers, with (S)-warfarin being 3–5 times more potent as an anticoagulant.
- (S)-Warfarin is metabolized by CYP2C9 (hydroxylation to 7-hydroxywarfarin), while (R)-warfarin is metabolized by CYP1A2 and CYP3A4.
- $$\text{(S)-Warfarin} \xrightarrow{\text{CYP2C9}} \text{7-Hydroxy-(S)-warfarin}$$
- $$\text{(R)-Warfarin} \xrightarrow{\text{CYP1A2/CYP3A4}} 6\text{-Hydroxy-(R)-warfarin or } 10\text{-Hydroxy-(R)-warfarin}$$
- Clinical Relevance: Slower metabolism of (S)-warfarin in CYP2C9 poor metabolizers increases bleeding risk, requiring careful monitoring.

1.4 Other Factors

- *Disease States:* Liver or kidney dysfunction reduces metabolic capacity.
- *Drug Interactions:* Enzyme inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole) alter metabolism rates.
- *Diet and Environment:* Nutritional status or exposure to toxins can influence enzyme expression.

2 Unit Summary: Key Concepts and Clinical Correlations

Unit I introduced foundational concepts in medicinal chemistry, emphasizing the interplay between physicochemical properties, drug metabolism, and therapeutic outcomes. Below is a summary of key topics and their clinical relevance.

2.1 History and Development of Medicinal Chemistry

- *Key Points:* Evolved from ancient herbal remedies to modern rational drug design, with milestones like Ehrlich's chemotherapy and the development of synthetic drugs.
- *Clinical Correlation:* Historical advancements enable targeted therapies, improving safety and efficacy.

2.2 Physicochemical Properties in Relation to Biological Action

- *Ionization:* Governed by pKa and the Henderson-Hasselbalch equation, affects absorption (e.g., aspirin's ionization in stomach vs. blood).
- *Solubility:* Influences dissolution rate; strategies like salt formation enhance bioavailability.
- *Partition Coefficient:* Log P determines lipophilicity, impacting CNS penetration.
- *Hydrogen Bonding:* Facilitates drug-receptor interactions.
- *Protein Binding:* Affects drug distribution and half-life (e.g., warfarin's high albumin binding).
- *Chelation:* Enhances drug activity in metal-binding drugs (e.g., tetracyclines).
- *Bioisosterism:* Allows structural modifications to improve potency or reduce toxicity.
- *Optical and Geometrical Isomerism:* Enantiomers (e.g., warfarin) and isomers (e.g., tamoxifen) exhibit different activities.
- *Clinical Correlation:* Optimizing physicochemical properties ensures effective drug delivery and action.

2.3 Drug Metabolism

- *Phase I:* Oxidation, reduction, hydrolysis (e.g., CYP450-mediated metabolism of warfarin).
- *Phase II:* Conjugation (e.g., glucuronidation of morphine) increases polarity for excretion.
- *Factors Affecting Metabolism:* Age, genetics, and stereochemistry modulate drug clearance and efficacy.
- *Clinical Correlation:* Understanding metabolism guides dosing adjustments, especially for drugs like warfarin with enantioselective metabolism.

2.4 Clinical Example - Warfarin

- *Structure:* Chiral coumarin derivative, with (S)- and (R)-enantiomers.
- *Pharmacokinetics:* High protein binding (99
- *Clinical Use:* Anticoagulant for atrial fibrillation, deep vein thrombosis.
- *Metabolism Factors:*
  - *Age:* Elderly patients require lower doses due to reduced hepatic clearance.
  - *Genetics:* CYP2C9 polymorphisms alter (S)-warfarin metabolism, impacting dosing.
  - *Stereochemistry:* (S)-Warfarin's faster metabolism by CYP2C9 vs. (R)-warfarin affects therapeutic monitoring.
- *Clinical Relevance:* Personalized dosing based on age, genetics, and stereochemistry minimizes bleeding risks.

3 Key Learning Points

- Age influences drug metabolism through changes in enzyme activity and organ function, as seen with warfarin in elderly patients.
- Genetic polymorphisms (e.g., CYP2C9) cause variability in drug metabolism, necessitating pharmacogenomic testing.
- Stereochemistry leads to enantioselective metabolism, impacting drug efficacy and safety (e.g., (S)- vs. (R)-warfarin).
- Unit I concepts (history, physicochemical properties, metabolism) provide a foundation for designing drugs with optimized pharmacokinetic and therapeutic profiles.