PHARMACOKINETICS

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Pharmacokinetics

what the body does to the drug?

- Absorption
- Distribution
- Metabolism
- Excretion.

is the **chemical alteration** of a drug in the body, mainly by **enzymes**, to make it easier for elimination (excretion).

Drug Biotransformation (METABOLISM)

- **The importance of biotransformation** is the conversion of unionized drugs to ionized, water-soluble metabolites, which are easily excreted.
- **The liver** is the main organ of metabolism but can also occur in other organs like lung, kidney and intestine.

Consequences of drug metabolism

1. Convert active drug to inactive metabolite (most drugs)
2. Convert inactive prodrug into active drug

   e.g. enalapril → enalaprilat (active)
3. Convert active drug to active metabolite

   e.g. codeine → morphine.
4. Convert drugs to toxic metabolites

e.g. Halothane & Paracetamol ---- hepatotoxic epoxides.

Biotransformation reaction

Phase I

- oxidation, reduction hydrolysis

Phase II

- Biosynthetic reactions "conjugation"

Phase I

oxidation by Cytochrome P450 (CYP).

active drug to inactive

prodrug to active drug

water soluble

not water soluble

Excreted by the kidney

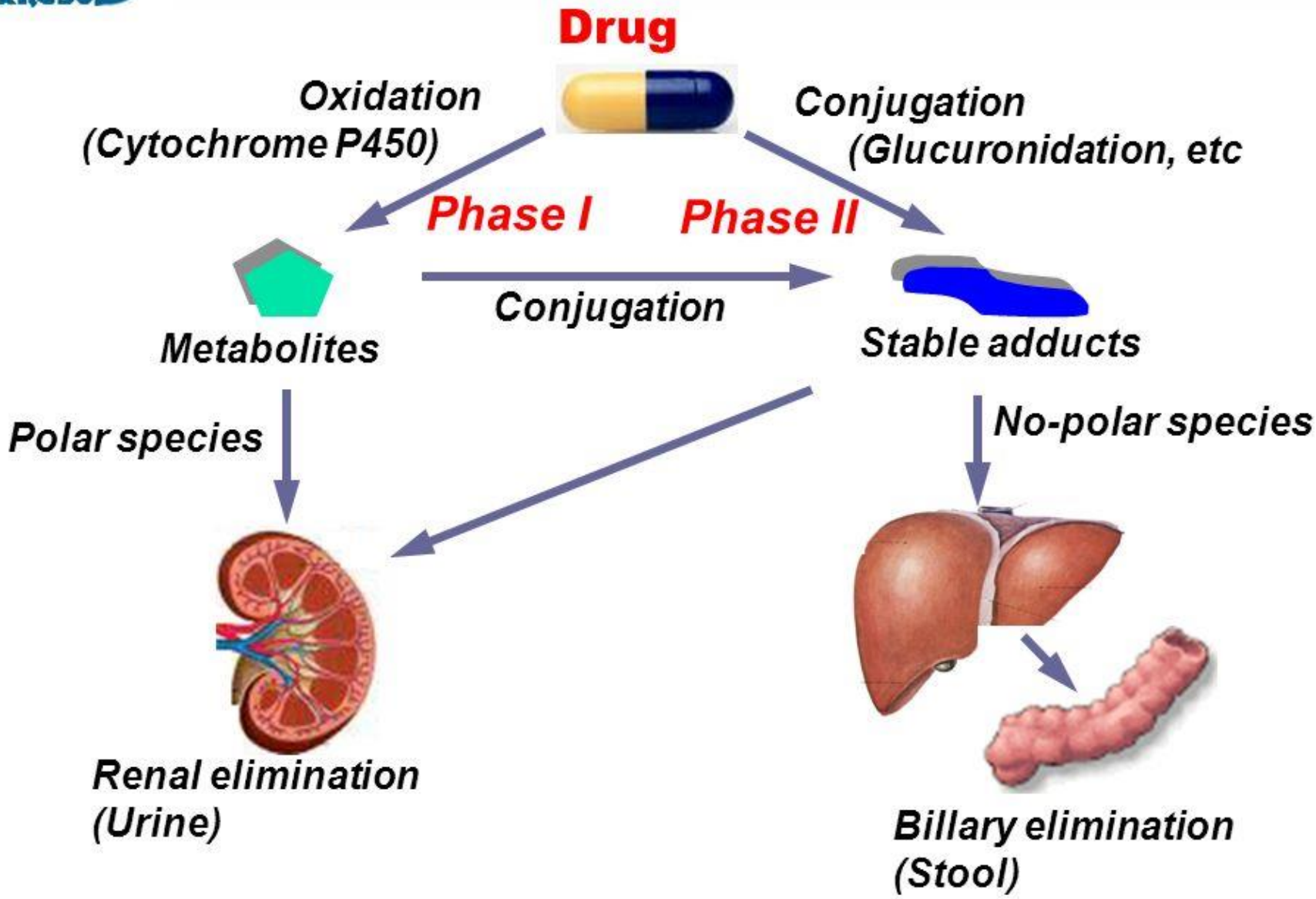
Enters phase II.

Phase II (biosynthetic)

"conjugation" reactions

- An endogenous substrate e.g., glucuronic acid, sulfate, glutathione, amino acids, or acetate is conjugated with the parent drug or its phase I metabolite.
- This results in the formation of water-soluble and rapidly eliminated conjugates..

Phases of metabolism



Factors affecting biotransformation

1. Physiological factors :age, Sex.
2. Nutritional state and habits
3. Pathological factors :liver cell failure.
4. Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast acetylators.
5. Enzyme induction & enzyme inhibition.

1- Physiological factors: age, Sex.

Newborns and infants: Enzymes are immature → slow metabolism.

- **Elderly:** Reduced liver size and blood flow → slower metabolism.
- **Adults (middle-aged):** Normal enzyme activity.
- Hormonal differences affect enzyme expression.
- Some drugs are metabolized faster in **men** (due to higher CYP activity).
- **Pregnancy** can alter metabolism due to hormonal changes.

2. Nutritional Status

- Malnutrition ↓ enzyme synthesis → slow metabolism.
- High-protein diets may increase enzyme activity.
- Smoking, pollutants, and pesticides can induce hepatic enzymes which

May reduce the effectiveness of other drugs.

2. Pathological factors: liver cell failure.

- **Hepatitis, cirrhosis, or liver cancer** reduce enzyme activity.
- Leads to **accumulation** of drugs → toxicity risk.
- **Decreased hepatic blood flow (e.g., heart failure, shock) reduces metabolism.**

3. Pharmacogenetic variation in metabolizing enzymes

genetic differences among individuals influence **drug metabolism**, **efficacy**, and **toxicity**.

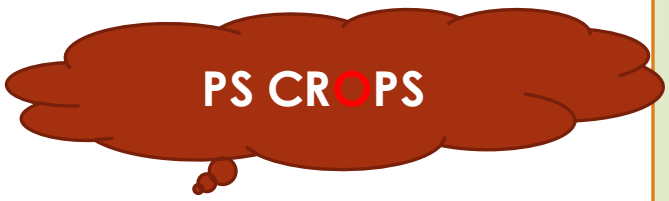
These variations are mainly due to **polymorphisms (gene mutations)** that alter the **activity of drug-metabolizing enzymes**, especially those in the **Cytochrome P450 (CYP)** system.

Slow acetylators of **isoniazid** → higher risk of toxicity.

Enzyme	Drug Affected	Variation Effect	Clinical Consequence
CYP2D6	Codeine	• slow metabolizers can't convert codeine → morphine • Rapid metabolizers	↓ Analgesia or toxicity
CYP2C9	Warfarin, Phenytoin	Slow metabolism	↑ Drug levels → bleeding (warfarin), toxicity (phenytoin)
N-acetyltransferase 2 (NAT2)	Isoniazid, Hydralazine, Procainamide, Sulfonamides	Slow acetylators → slow drug inactivation Fast acetylators →	↑ Toxicity: peripheral neuropathy, lupus-like reaction may need higher doses.
Thiopurine methyltransferase (TPMT)	Azathioprine, 6-mercaptopurine	Deficiency → impaired inactivation	↑ Bone marrow toxicity
Pseudocholinesterase	Succinylcholine	Enzyme deficiency	Prolonged apnea after anesthesia

Enzyme induction

- Many drugs can induce (increase activity and number) of microsomal enzymes, resulting in an increased rate of metabolism of the inducing drug as well as other drugs metabolized by the same enzymes microsomal enzymes. (This process leads to faster metabolism of drugs)



- **Some inducing drugs**: **P**henobarbitone, **p**henytoin, **r**ifampicin, **c**arbamazepine, **s**moking (nicotine)

Consequences of enzyme induction

1. Increase the metabolism of the inducing drugs.

This leads to tolerance e.g., phenobarbitone.

2. Drug interactions:
   - ❑ Rifampicin enhances the metabolism of warfarin.
   - ❑ Antiepileptics increase the metabolism of each other.
3. Prolonged use of enzyme inducers may produce rickets or osteomalacia due to increased metabolism of vitamin D.

❖ Enzyme induction is reversible. It occurs over a few days and passes off over 2 - 3 weeks after withdrawal of the inducer.

Enzyme inhibition

- Many drugs inhibit the activity of microsomal enzymes, resulting in decreased rate of metabolism of other drugs i.e., potentiate their pharmacological actions.

- **Some enzyme Inhibitor drugs**
  - (S) Sodium valproate, (I) Isoniazid, (C) Cimetidine, (K) Ketoconazole, (F) Fluconazole, (A) Amiodarone, (C) Ciprofloxacin, (E) Erythromycin (macrolides), (S) Sulfonamides, (C) Chloramphenicol (M) Metronidazole

Consequences of enzyme inhibition on metabolized drugs

1) Exaggerated pharmacological actions.

2) Exaggerated adverse effects.

3) Drug interactions.

Feature	Induction	Inhibition
Effect on enzyme	↑ synthesis/activity	↓ activity
Drug metabolism	↑ Faster	↓ Slower
Drug effect	↓ Decreased	↑ Increased
Toxicity risk	↓ Lower	↑ Higher
Duration of effect	Shorter	Longer


TO BE
CONTINUED