PHARMACOKINETICS

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Pharmacokinetics

what the body does to the drug?

- **Absorption**
- **Distribution**
- Metabolism
- Excretion.

Drug Biotransformation (METABOLISM)

- **The importance of biotransformation** is the conversion of unionized drugs to ionized, water soluble metabolite which is easily excreted.
- **The liver** is the main organ of metabolism but can 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

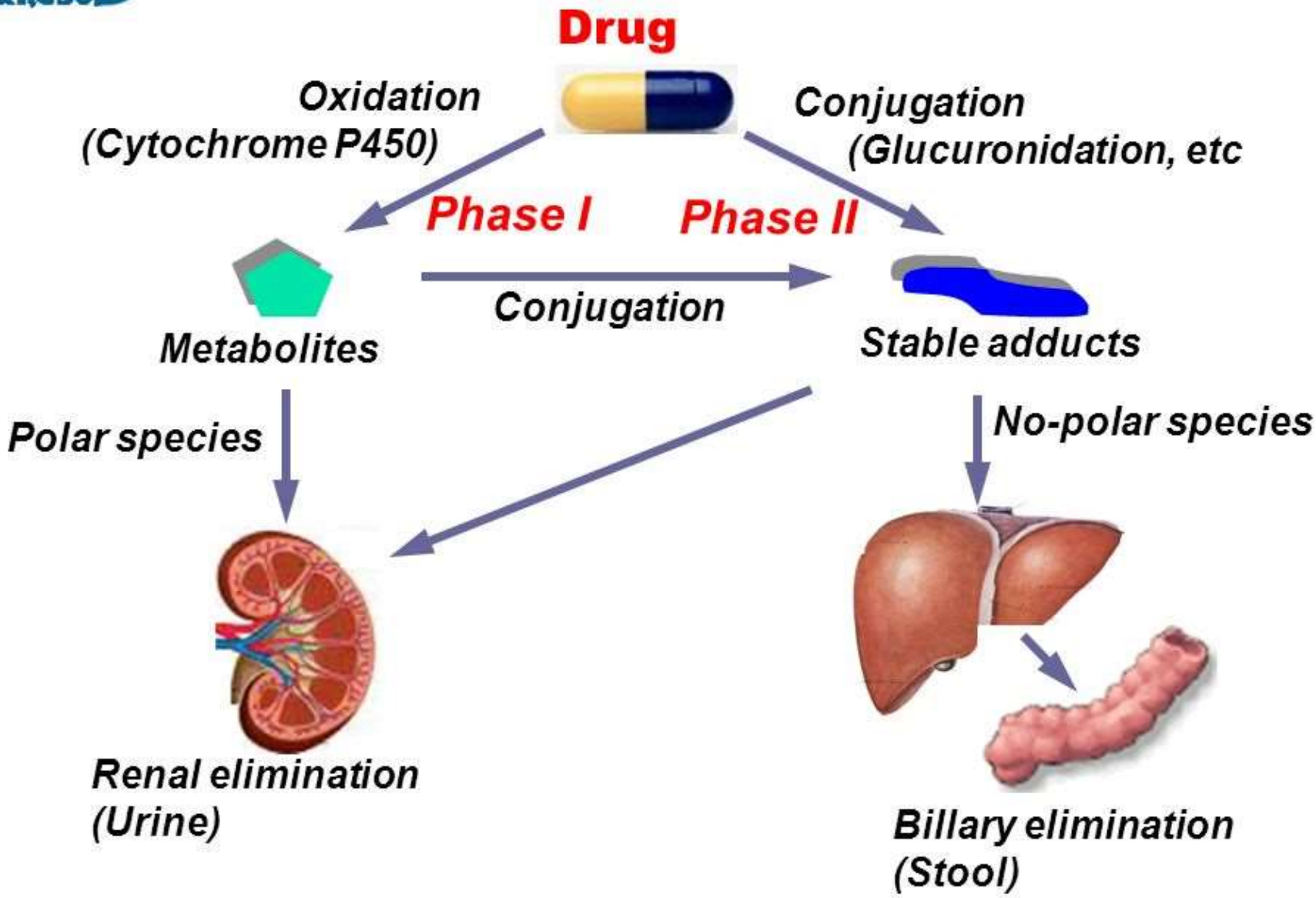
Enters phase II.

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 result in formation of water soluble and rapidly eliminated conjugates..

Phases of metabolism



Factors affecting biotransformation

1. Physiological factors :age, Sex.

2. Pathological factors :liver cell failure.

3. Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast acetylators.

4. Enzyme induction & enzyme inhibition.

Enzyme induction

- Many drugs are able to induce (increase activity and number) of microsomal enzymes resulting in increased rate of metabolism of the inducing drug as well as other drugs metabolized by the same microsomal enzymes.
- **Some inducing drugs** : Phenobarbitone, phenytoin, nicotine, rifampicin, carbamazepine.

Consequences of enzyme induction:

1. Increase metabolism of the inducing drugs. This leads to tolerance e.g. phenobarbitone.
2. Drug interactions:
   - ❑ Rifampicin enhances 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 few days and passes off over 2 - 3 weeks after withdrawal of inducer.

Enzyme inhibition

- Many drugs inhibit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs i.e. potentiate their pharmacological actions.
- **Some enzyme Inhibitor drugs**
  - Erythromycin, Clarithromycin, Cimetidine, Contraceptive pills

Consequences of enzyme inhibition on metabolized drugs

1) Exaggerated pharmacological actions.

2) Exaggerated adverse effects.

3) Drug interactions.


TO BE
CONTINUED