NOVA

Charting New Horizons in Education

Pharmacokinetics III

05

pharmacology

Created by : Dr Farah Breik

Pharmacokinetics

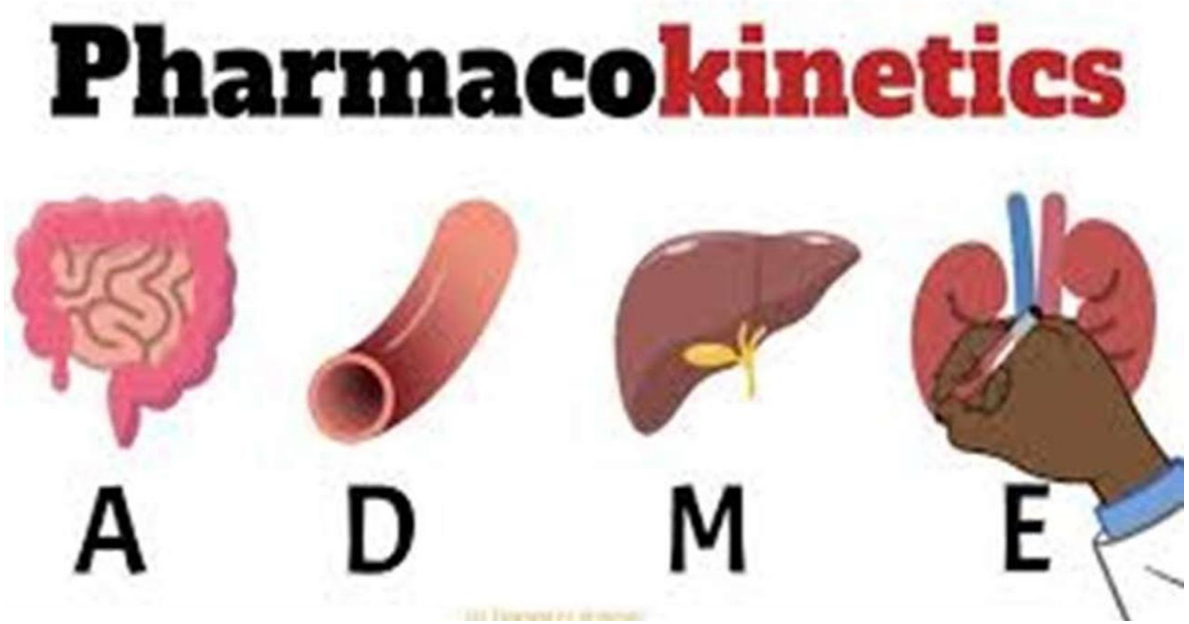
what the body does to the drug?

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

- Convert active drug to inactive metabolite
  (most drugs)
- Convert active drug to active metabolite

  e.g. codeine to morphine.
- Convert inactive prodrug into active drug

  e.g. enalapril to enalaprilat (active)
- Convert drugs to toxic metabolites

  e.g. : Halothane & Paracetamol to

hepatotoxic epoxides.

PHASE 1

- Oxidation or reduction or hydrolysis
  - The most important

PHASE 2

- Biosynthetic reactions "conjugation"

Most common CYP450:
CYP3A4
CYP2D6

Phase I

Oxidation by cytochrome p450

Active drug to inactive

Prodrug to active drug

Water soluble

Not water soluble

Excreted by the kidney

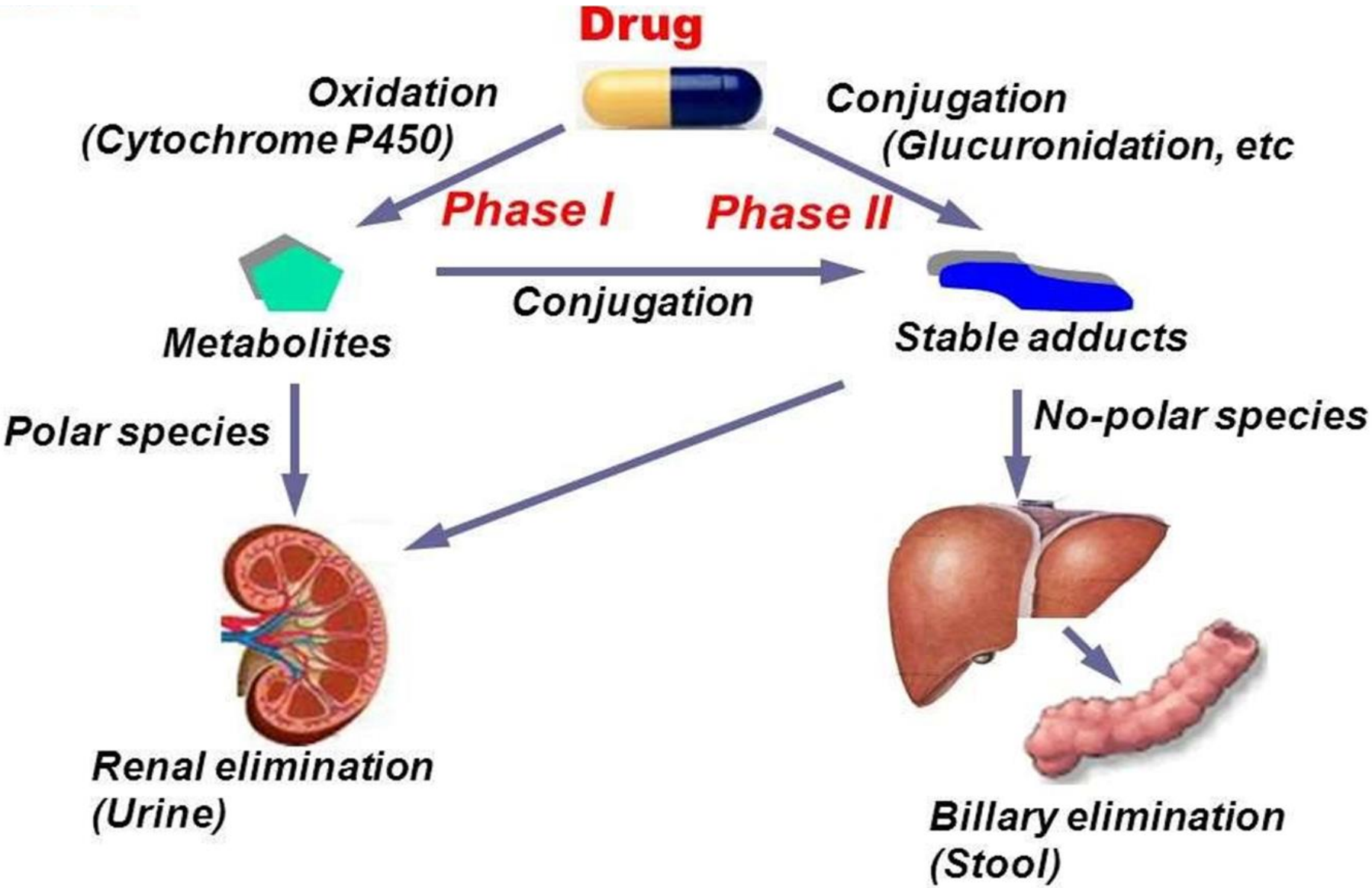
Enters phase II

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 Drug metabolism:



Factors affecting biotransformation:

- Physiological factors :

1- age (CYP450 enzyme is low in infants, reaches its peak in adults, and then decreases with age in the elderly)

2- Sex

- Pathological factors :liver cell failure.

- Pharmacogenetic variation in metabolizing

- enzymes e.g. slow and fast acetylators.

(if CYP3A4 genetically absent ,50% of drugs will not be metabolized)

- 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

✓carbamazepine.

✓Nicotine

✓Rifampicin.

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:

1. Exaggerated pharmacological actions.

2. Exaggerated adverse effects.

3. Drug interactions.

«Education is the passport to the future, for tomorrow belongs to those who prepare for it today»

- Maclom X-

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