

# Pharmacokinetics: Biotransformation of Drugs

VPT: Unit I; Lecture-15  
(Dated 05.11.2020)



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# Mechanisms of Drug Elimination

- Biotransformation (metabolism) and Excretion.
- Lipid solubility and degree of ionization.
- Lipid solubility : A prerequisite for biotransformation of drugs by the hepatic microsomal enzyme system.
- Polar drugs and many drug metabolites are excreted by the kidneys.
- Apart from liver, metabolism of drugs takes place in blood plasma and lumen of the gut as well as in other tissues (intestinal mucosa, kidney & lung).

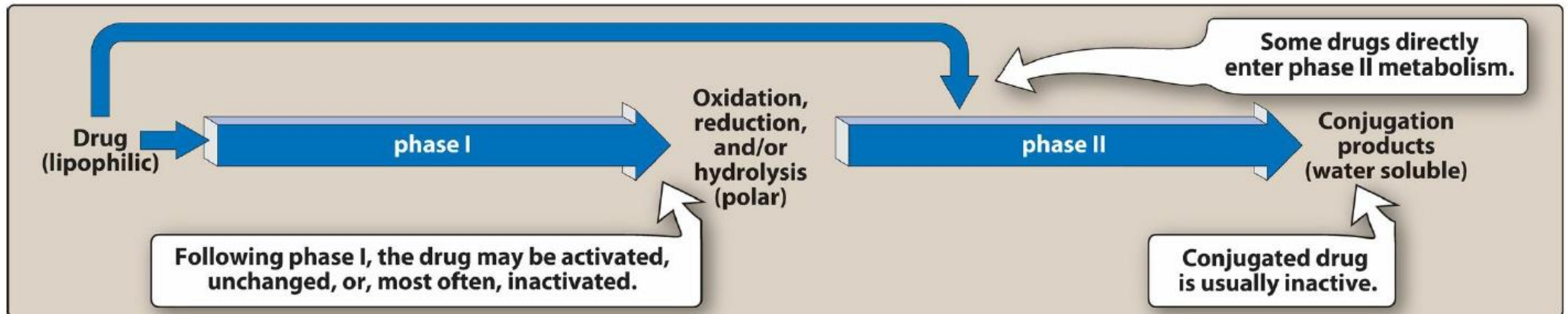
# Drug Metabolism (Biotransformation)

- Drugs undergo metabolic changes in the body for their excretion.
- **Products of biotransformation:** Generally less lipid soluble and more polar in nature. These properties help excretion of drugs.
- Mostly **hydrophilic drugs are not biotransformed.**  
Example - Streptomycin, Neostigmine etc.

# Drug Metabolism (Biotransformation)

contd...

- Drug metabolism has been generally divided into two types of reactions, termed phase I and phase II reactions.



# Drug Metabolism (Biotransformation)

contd...

- The initial phase (Phase I): Non-synthetic reactions like Oxidation, Reduction & Hydrolysis.
- The second phase (Phase II): The synthetic reactions (conjugations).
- **Phase I biotransformations:** Usually unmask or introduce into the drug molecule polar groups such as -OH, -SH, -COOH, and -NH<sub>2</sub>.

# Drug Metabolism (Biotransformation)

contd...

- The **functional groups** enable the compound to undergo **conjugation with endogenous substances** such as glucuronic acid, acetate (acetylation), sulphate (sulphuric acid ester formation) and various amino acids (primarily glutathione, cysteine and glycine).
- The drug conjugates formed are water soluble and almost invariably inactive pharmacologically.
- **Metabolites of phase I biotransformation** reactions may be pharmacologically active or inactive, but **phase II metabolites** are mostly inactive.

# Biotransformation reactions may lead to :-

- ✓ **Inactivation:** e.g. Phenobarbitone, Morphine, Chloramphenicol etc.
- ✓ **Active metabolite from an active drug:** e.g. Enrofloxacin converted to ciprofloxacin.
- ✓ **Activation of the inactive drug:** Activation of 'Prodrug'.

Prodrug

Levodopa

Prontosil

Active form

Dopamine

Sulfanilamide

# Phase I (Non-synthetic) Biotransformation reactions

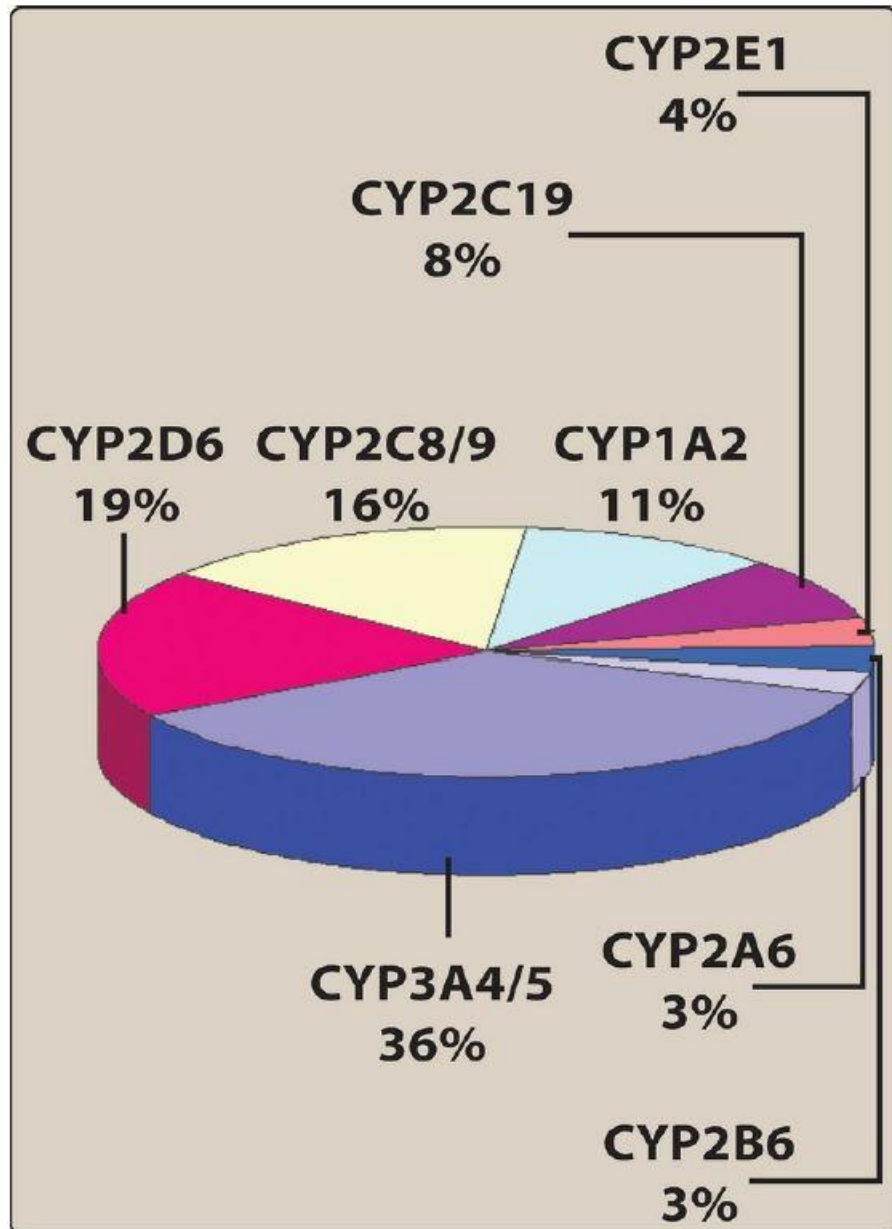


## (1) OXIDATION:

- The most important drug metabolizing reactions.
- Oxidation reactions are mostly carried out by a group of monooxygenases in the **liver**, which in the final step involve a **Cytochrome P-450** haemoprotein, **NADPH**, **cytochrome P-450** reductase and  $O_2$ .
- These enzymes are also known as **microsomal oxidases** or **mixed function oxidases**.

# Cytochrome P450 (CYP) system

- The Cytochrome P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (drugs, carcinogens, and environmental pollutants).
- CYP is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and GI tract.
- Nomenclature: The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A. A second number indicates the specific isozyme, as in CYP3A4.



**Figure:** Relative contribution of cytochrome P450 (CYP) isoforms to drug biotransformation.

# CYP Inducers

- The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions.
- Certain drugs (for example, phenobarbital, rifampin, and carbamazepine) are capable of inducing CYP isozymes.
- This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, often with concurrent loss of pharmacologic effect.

Isozyme: CYP2C9	
COMMON SUBSTRATES	INDUCERS
<i>Celecoxib</i> <i>Glimepiride</i> <i>Ibuprofen</i> <i>Phenytoin</i> <i>Warfarin</i>	<i>Carbamazepine</i> <i>Phenobarbital</i> <i>Rifampin</i>

Isozyme: CYP2D6	
COMMON SUBSTRATES	INDUCERS
<i>Fluoxetine</i> <i>Haloperidol</i> <i>Paroxetine</i> <i>Propranolol</i>	None*

Isozyme: CYP3A4/5	
COMMON SUBSTRATES	INDUCERS
<i>Carbamazepine</i> <i>Cyclosporine</i> <i>Erythromycin</i> <i>Nifedipine</i> <i>Simvastatin</i> <i>Verapamil</i>	<i>Carbamazepine</i> <i>Dexamethasone</i> <i>Phenobarbital</i> <i>Phenytoin</i> <i>Rifampin</i>

## Various oxidative reactions of drugs :

<i>Oxidative reaction</i>	<i>Drug</i>	<i>Metabolite</i>
Aromatic hydroxylation	Phenylbutazone*	Oxyphenbutazone *
Aliphatic oxidation	Pentobarbital *	Pentobarbital alcohol
O-dealkylation	Phenacetin *	Acetaminophen *
N-dealkylation	Diazepam *	N-desmethyldiazepam *
Oxidative deamination	Amphetamine *	Phenylacetone
Desulfuration	Parathion	Paraxon *

\* Pharmacologically active compound.

## (2) REDUCTION:

- Microsomal reductions occur less frequently than oxidations, but can take place in drugs which contain - disulphide (S=S), azo (N=N), or nitro (-NO<sub>2</sub>) groups.
- These reactions are converse of oxidations and involve cytochrome P-450 enzymes working in opposite direction. The enzymes involved are reductases.
- Reductive biotransformation reactions are as follow:

Drug

Prontosil

Chloramphenicol\*

Metabolite

Sulfanilamide \*

Inactive amine metabolites

\*Pharmacologically active compound.

### (3) HYDROLYSIS:

- Hydrolysis is an important metabolic pathway for compounds with an **ester linkage (-COO-)** or an **amide (-CONH-)** bond.
- Hydrolytic cleavage reactions can take place in **liver, intestines, plasma** and other tissues.

Examples: Hydrolysis of -

Acetylcholine (ACh) by acetylcholinesterase (AChE)

Suxamethonium (plasma) by plasma pseudocholinesterase

Atropine (plasma) by atropinase

Procaine (plasma) by plasma cholinesterase.

Lignocaine (liver) by non-microsomal hepatic amidase.

# Phase II (Synthetic/ Conjugation) Biotransformation reactions



✓ Synthetic reactions may take place when a drug or phase I metabolite contains a chemical group such as hydroxyl (-OH), carboxyl (-COOH), amino (-NH<sub>2</sub>) or sulfhydryl (-SH) and is suitable for combining with a natural compound provided by the body to form readily excreted water soluble polar metabolites.

✓ **Conjugating agents** include -

Glucuronic acid,	Glutathione,
Glycine,	Cysteine,
Methionine	Sulphate &
Acetate.	

- These conjugating agents do not, however, react directly with the drug or phase I metabolite but do so either in an activated form or with an activated form of the drug (as an example, acetyl CoA rather than acetate).
- Conjugation reactions have high energy requirement.

## (1) GLUCURONIDE CONJUGATION :

- In liver, by microsomal enzyme glucuronyl transferase.
- The **cat** synthesizes glucuronide conjugates at a slow rate, as this **species is deficient in the transferring enzyme, glucuronyl transferase** .
- The activated form of glucuronic acid is the nucleotide - **Uridine diphosphate glucuronic acid (UDPGA)**.
- **Examples** - Morphine, salicylates, acetaminophen, chloramphenicol, sulphadimethine and phase-1 metabolites of diazepam (oxazepam), phenylbutazone (oxyphenbutazone).
- The glucuronyl conjugates are extensively excreted in the **bile**.

## (2) SULPHATE CONJUGATION :

- In liver, soluble fraction of liver.
- Capacity for sulphate conjugation in the pig is limited.
- Examples - Phenol, aliphatic alcohols, isoproterenol, ascorbic acid etc. and endogenous compounds like chondroitin, heparin etc.

### (3) ACETATE CONJUGATION :

- Reticuloendothelial cells rather than parenchymal cells of liver, spleen, lungs and intestinal mucosa.
- Dogs and foxes do not acetylate.
- Acetylation reaction takes place in two stages - (i) formation of Acetyl CoA (ii) nucleophilic attack by the amino - containing compound on the acetylated enzyme.
- Examples - Sulphonamide compounds etc.
- Acetylation decreases water solubility as well as lipid solubility of metabolites. e.g. Acetylation of sulphonamides lead to chances of crystalluria.

**Thank You**

