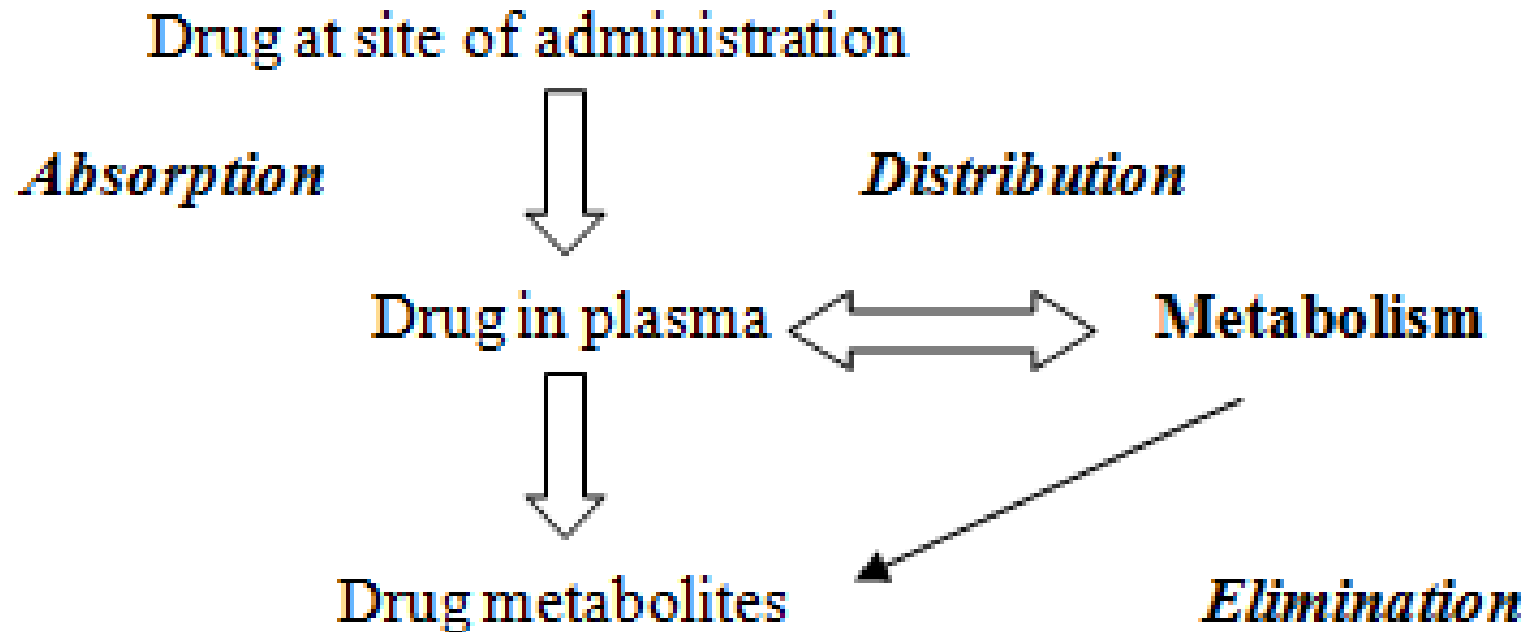


Biotransformation



Biotransformation



Biotransformation

- Alteration of a drug within a living organism
- Metabolic transformation: Mitochondrial, microsomal, cytosolic
- Inactive to active: L- dopa – Dopamine
- Active to inactive: Chloramphenicol conjugate
- Active to active:
 - More active: Diazepam – Oxazepam
 - Different activity: Pethidine - Norpethidine



Biotransformation

- Excretion unchanged – Aminoglycosides
- Metabolism : less polar, lipid soluble – more polar, water soluble
- Spontaneous change into other substances
 - Mechlorethamine – active ethylniminium cations at slightly alkaline pH
 - Atracurium – Hoffman reaction



Prodrug

- Precursor drug that itself has little or no biological activity
- Metabolized to a pharmacologically active metabolite

First pass metabolism/ Presystemic metabolism

- Before reaching systemic circulation gets metabolized
- Decreased BA, diminished therapeutic response
- Bypassed: IV, sublingual route



Chemical Pathways of Biotransformation

Phase I

- Metabolite: active/inactive
- Degradative reactions
- Small non polar/polar metabolite
- Mainly microsomal
- Few non- microsomal

Phase II

- Metabolite inactive
- Synthetic /conjugation reactions
- Polar metabolite
- Mitochondrial, microsomal, cytoplasmic



PHASES OF DRUG METABOLISM

PHASE I REACTION	PHASE II REACTION
1. Degradative reaction	1. Synthetic reaction
2. Introduction of functional group (-OH, -NH ₂ , -SH, -O -, -COOH)	2. Conjugates phase 1 metabolite with glucuronic acid, sulfate, acetyl, methyl groups.
3. Mainly microsomal	3. Microsomal, Mitochondrial & Cytoplasmic
4. Metabolites formed may be smaller, polar/non-polar Active/Inactive	4. Metabolites formed are usually larger, polar, water soluble & Inactive



Drug Metabolizing enzymes

Microsomal enzymes

- Located on smooth ER, lungs, kidney, intestinal mucosa
- MFOs/ CYP450
- CYP1A1,2
- CYP3A4,5
- CYP2C8, 9

Non - microsomal enzymes

- Present in cytoplasm, mitochondria, plasma
- MAO
- Esterases
- Amidases
- Transferases
- Conjugases



Phase I reactions - oxidations

Microsomal Oxidation

- **Aromatic hydroxylation**
 - Phenobarbitone – P-hydroxy phenobarbitone
- **Aliphatic hydroxylation**
 - Pentobarbitone – Hydroxy pentobarbitone
- **N – dealkylation**
 - Morphine – normorphine
 - Mephobarbitone - phenobarbitone



Phase I reactions

Microsomal Oxidation

- **O -dealkylation**
 - Codeine - morphine
- **S -dealkylation**
 - 6-methyl thiopurine - mercaptopurine
- **S – Oxidation**
 - Chlorpromazine - Chlorpromazine sulfoxide



Phase I reactions

Microsomal Oxidation

- **N – oxidation**
 - Trimethylamine – Trimethylamine N - oxide
- **Deamination**
 - Amphetamine – phenylacetone derivative
- **Desulfarisation**
 - Parathion - paraoxon



Phase I reactions

Non - microsomal Oxidation

- **Mitochondrial oxidation**
 - Adrenaline by MAO to VMA
- **Cytoplasmic oxidation**
 - Alcohol by alcohol dehydrogenase to acetaldehyde
- **Plasma oxidation**
 - Histamine by histaminase to IAA



Phase I reactions - Reductions

Microsomal reductions

- **Nitro reduction**
 - Chloramphenicol to its arylamine metabolite
- **Azo reduction**
 - Protonsil to sulfanilamide
- **Keto reduction**
 - Cortisone to hydrocortisone

Non – microsomal reductions

Chloral hydrate to trichloro ethanol



Phase I reactions - Hydrolysis

Microsomal hydrolysis

Pethidine to pethidinic acid by hepatic esterase

Non microsomal hydrolysis

- Esterases, amidases, peptidase, protease, phosphatase
- Procaine – PABA
atropine – Tropic acid
- Hydrolysis of beta lactam ring of penicillin



Phase II Reactions

Microsomal Conjugation

- **Glucuronide Conjugation:**
- Parent drugs/phase I metabolites
- Containing phenolic, alcoholic, -COOH, -NH₂, mercapto group
- Polar readily excreted, often inactive
- Morphine, paracetamol, aspirin, sulfonamide, bilirubin



Phase II Reactions

Non microsomal Conjugations:

N –Acetyl Conjugation (In cytosol)

- Isoniazid, PAS, dapson, sulfonamides, histamine

Sulfate conjugation (In cytosol)

- Phenolic, alcoholic, aromatic amines undergo
- Aspirin, methyldopa, paracetamol, chloramphenicol

Aminoacid conjugation (In mitochondria)

- Aspirin, benzoic acid, nicotinic acid



Phase II Reactions

Non microsomal Conjugations:

Methyl Conjugation (In cytosol)

- Many catecholamines, histamine

Glutathione conjugation (In cytoplasm)

- Epoxides, NO₂ containing drugs, hydroxylamines
- Ethacrynic acid, sulfobromophthalein

Ribosides & riboside phosphate

- Aspirin, benzoic acid, nicotinic acid

