METABOLISM - I

Dr. R. Jamuna Rani  MD,  
Professor & HOD,  
Department of Pharmacology.
INTRODUCTION

- Most drugs are treated by the body as foreign substances (xenobiotics). Metabolism is a general term for chemical transformation that occur within the body by two ways.
  - By reducing lipid solubility
  - By altering biological activity
Drug metabolising enzymes were developed during evolution to enable the body to dispose lipid soluble substances such as hydrocarbons, steroids and alkaloids that are ingested with food.

THEREFORE METABOLIC REACTIONS TEND TO MAKE A DRUG MOLECULE MORE WATER SOLUBLE AND SO FAVOR ITS ELIMINATION IN THE URINE.
ALTERING BIOLOGICAL ACTIVITY

- CONVERSION ACTIVE DRUG – INACTIVE DRUG
- CONVERSION ACTIVE DRUG – ACTIVE METABOLITE
- CONVERSION OF PHARMACOLOGICALLY INACTIVE DRUG TO ACTIVE SUBSTANCE - PRODRUG
<table>
<thead>
<tr>
<th>PRO DRUG</th>
<th>ACTIVE DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Enalaprilat</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Bacampicillin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>5-Aminosalicylic acid</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Aldophosphamide, Phosphoramidine mustard, acrolein</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Zidovudine triphosphate</td>
</tr>
</tbody>
</table>
• The two phases of drug metabolism
  Phase 1                     Phase 2
  Drug → Derivative → Conjugate
  Oxidation                   Conjugation
  Hydroxylation oxygenations at C, N and S
  Dealkylation
  Deamination
  Eg. Imipramine
EXAMPLES OF PHASE I & PHASE II REACTIONS

IMIPRAMINE

Demethylation

Dealkylation

Hydroxylation

Conjugation

Urinary Excretion
OXIDATIVE REACTIONS

• N – Dealkylation (eg.) Diazepam
• O – Dealkylation (eg.) Codeine
• Aliphatic hydroxylation (eg.) Cyclosporin
• Aromatic hydroxylation (eg.) Phenytoin
• N – Oxidation (eg.) Chlorpheniramine
• S – Oxidation (eg.) Chlorpromazine
• Deamination (eg.) Amphetamines
• CYCLIZATION: This is formation of ring structure from a straight chain compound, e.g. Proguanil

• DECYCLIZATION: This is opening up of ring structure of the cyclic drug molecule, e.g. barbiturates, phenytoin. This is generally a minor pathway.
• Reduction: eg. Chloramphenicol, Halothane.
• Hydrolysis: eg. Procaine, lidocaine.
SYNTHETIC REACTIONS

- Glucuronide Conjugation: eg. Acetaminophen (paracetamol), Morphine, metronidazole, Chloramphenicol - conjugate with UDP-glucuronosyltransferase and form UDP-glucuronide conjugate.
- Endogenous substances like bilirubin, thyroxine, fatty acids and steroids are excreted through glucuronide conjugation.
- Enterohepatic cycling: OCP oral contraceptives and pentaerythritol tetra nitrate.
- Energy dependent process.
UDP-α-glucuronide

Glucuronyl transfer → UDP-glucuronyl transferase

DRUG → Glucuronide

Drug – β – glucuronide conjugate
• ACETYLATION: Compounds with amino and hydrazine group undergo acetylation with the help of N-acetyltransferase. Eg. INH, sulfonamides, dapsone.

• Methylation occurs with the help of methyltransferase eg. Norepinephrine – Normetanephrine

• Sulfate conjugation occurs with the help of sulfotransferase eg. Salicylic acid

• Glutathione conjugation with the help of glutathione S-transferase eg. N-Acetylbenzoquinoneimine.
• Ribonucleoside / nucleotide synthesis: Activation of purine and pyrimidine antimetabolites used in cancer chemotherapy

• Hoffman elimination: Inactivation of drug by body fluids by spontaneous molecular rearrangement without enzyme (e.g.) Atracurium.
Paracetamol is primarily metabolized by glucuronide conjugation and the minor metabolite N-acetyl – p – benzoquinoneimine by glutathione conjugation.

Phase I reactions are mediated by oxygenases (flavin containing monooxygenases and epoxide hydrolases).

Phase II reactions are mediated by transferases.
• Reversal order of phases: Not all drugs undergo Phase I and II without order eg. INH first acetylated and hydroxylated to isonicotinic acid.
<table>
<thead>
<tr>
<th>Active drug</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitoxin</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Codeine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Desmethyl diazepam oxazepam</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Canrenone</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Trichloroethanol</td>
</tr>
</tbody>
</table>
METABOLISM - II

Dr. R. Jamuna Rani  MD,  
Professor & HOD,  
Department of Pharmacology.
<table>
<thead>
<tr>
<th>MICROSONOMAL</th>
<th>NON MICROSONOMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth endoplasmic reticulum of liver, kidney,</td>
<td>Cytoplasam &amp; hepatic cells and also in</td>
</tr>
<tr>
<td>intestinal mucosa and lungs</td>
<td>plasma</td>
</tr>
<tr>
<td>Monooxygenases (flavin monooxygenase &amp; Epoxide</td>
<td>They are flavoproteins. Oxidases, esterases,</td>
</tr>
<tr>
<td>hydrolases, cytochrome P450, glucuronyl transferase are microsomal enzymes</td>
<td>amidase, conjugases, transferases</td>
</tr>
<tr>
<td>They catalyse most of the oxidation, reduction, hydrolysis and glucuronide conjugation</td>
<td>They catalyse some oxidation, reduction, hydrolytic reaction and all conjugates except glucuronidation</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>They are inducible by drugs, diet and other agencies</td>
<td>Not induced by drugs, diet and other agencies</td>
</tr>
</tbody>
</table>
Both microsomal and non-microsomal enzymes are deficient in the newborn. Specially premature, making them more susceptible to many drugs eg. Chloramphenicol (gray baby syndrome)

Non microsomal enzymes exhibit GENETIC POLYMORPHISM eg. Pseudocholinesterase and acetyl transferase
• Amount and kind of drug metabolizing enzyme is controlled genetically and altered by environmental factors
• There is marked interspecies and interindividual differences are seen.
• Cats are deficient in glucuronyl transferase and Dogs are deficient in acetyl transferase
• Rate of metabolism is different in the human beings. There is six fold difference in the rate of metabolism in human beings
CYTOCHROME P450

• CYP450 important for metabolism of endogenous compounds steroids, lipids, thyroxine and bilirubin super family of enzymes. They are heme containing enzyme located in most of the cells especially in the liver and intestinal tract. The term P450 originates from the spectral peak produced at or near 450nm. When isoenzyme (in its reduced state) is treated with carbon monoxide.

CYP 3A4 - The family name is indicated by number 3, followed by capital letters A for the sub family, another number 4 is added to indicate the isoenzyme (gene).
<table>
<thead>
<tr>
<th>ISOENZYME P450</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>Theophylline</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Caffeine, Paracetamol, tacrine, theophylline</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Taxol</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Ibuprofen, phenytoin, tolbutamide, warfarin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Clozapine, codeine, debrisoquine, metoprolol</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Alcohol, enflurane, halothane</td>
</tr>
<tr>
<td>CYP3A4/5</td>
<td>Ciclosporin, losartan, nifedipine, terfenadine</td>
</tr>
</tbody>
</table>
DRUG DRUG INTERACTIONS

- Terfenadine, once popular antihistamine was removed from the market because its metabolism was blocked by CYP3A4 substrates such as erythromycin and grapefruit juice, produced arrhythmias (ventricular tachycardia)
• Human subjects can be grouped into extensive or poor metabolizers eg. metoprolol, poor metabolizers have altered Cyp2D6 enzyme and have low capacity to hydroxylate many drugs.
• Drugs that inhibit drug metabolising enzyme
  • Allopurinol
  • Amiodarone
  • Ciprofloxacin
• Clarithromycin
• Chloramphenicol
• Disulfiram
• Erythromycin
• Ketoconazole
• Isoniazid
• Metronidazole
• Metabolism of drug with high hepatic extraction is dependent on liver blood flow. Propranolol reduces the lidocaine metabolism by decreasing hepatic blood flow.

• Most drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein specially CYP450 and glucuronyl transferase.
• As a result rate of metabolism of inducing drug itself or other drug is increased
• Phenobarbitone, rifampin and glucocorticoids induce CYP3A isoenzymes
• Phenobarbitone and rifampin also induce CYP2D6
• INZ and chronic alcohol consumption induce – CYP2E1
• Polycyclic hydrocarbons like 3 – methyl cholangthrene and benzopyrene found in cigarette smoke, charcoal broiled meat and industrial pollutants induce CYP1A isoenzymes
• Other drugs which induce microsomal enzymes are chloralhydrate, griseofulvin, phenylbutazone, DDT – Dichloro diphenyl trichloroethane.

• Induction involves the microsomal enzymes in the liver as well as in the other organs

• Induction takes 4 – 14 days to reach its peak and is maintained till the inducing agent is being used.

• Once it is stopped it returns to original value over 1- 3 weeks
• Consequences of microsomal enzyme induction: decrease the intensity and duration of action of drug.
  - Failure of contraception with OCP
• It increases the toxicity of paracetamol at low doses
• Drug induces its own metabolism (auto induction) eg. Carbamazepine, rifampicin produces tolerance
• Endogenous substances are metabolised faster (steroids and bilirubin)
• Intermittent use of inducers will interfere with the treatment of antihypertensives, anti epileptics, oral hypoglycemic agents, anticoagulants
• Precipitate acute intermittent porphyria - increase porphyrin synthesis
• Interfere with chronic toxicity testing in animals
USES OF ENZYME INDUCTION

- 1. Congenital non haemolytic jaundice – phenobarbitone causes rapid clearance of bilirubin
- Phenytoin reduces the manifestations in cushing’s syndrome
- Chronic poisoning
- Liver disease
PRESYSTEMIC OR FIRST PASS METABOLISM

• This refers to metabolism of drug during its passage from the site of absorption to systemic circulation
• All orally administered drugs are exposed to drug metabolising enzymes in the intestinal wall and liver through portal vein
• The extent of first pass metabolism differs for different drugs
• Oral dose is considerably higher than sublingual and parenteral dose.
• There is individual variation in the oral dose due to the difference in the extent of first pass metabolism.
• Oral bioavailability is increased in liver disease.
• Oral bioavailability increase if another drug with high first pass metabolism is given concurrently eg. Chlorpromazine and propranolol.
DRUGS UNDERGOING FIRST PASS METABOLISM ARE

• Propranolol
• Glyceryl trinitrate
• Imipramine
• Levodopa
• Lignocaine
• Pethidine
• Dextropropoxyphene

Morphine
Aspirin
Verapamil
Salbutamol
Chlorpromazine
Labetalol
Pentazocine