Pharmacokinetics
Metabolism
Learning object

- Know the processes involved in ADME of drugs
- Know how these processes may affect the action of xenobiotics
- Appreciate how these processes can affect the outcome of the treatment of patients with drugs
- Appreciate how differences in these processes between patients can affect therapy
- Know how these processes have been exploited to improve therapy
- Be able to exemplify the above
BIOTRANSFORMATION (Metabolism)

- Chemical alteration of the drug in the body is called as **biotransformation**.

- It is needed to render
  Nonpolar (lipid-soluble) compounds
  \[\text{polar (Water soluble)}\]
  excreted in urine.
• Most Polar (hydrophilic drugs) e.g. Streptomycin
  little biotransformed
  excreted unchanged.
The primary site for drug metabolism is liver.

Others sites are:
- kidney
- intestine
- lungs
- Plasma
Biotransformation of drugs may lead to

Active drug \rightarrow \text{Inactive}

eg. ibuprofen, paracetamol

Inactivation-1
2. Active drug $\rightarrow$ Active metabolite

Eg.
- Morphine (Active) $\rightarrow$ Morphine-G glucuronide (active)
3. Inactive drug $\rightarrow$ Active drug

- eg. Prodrug such as:

  Levodopa $\rightarrow$ Dopamine
  (Inactive) $\rightarrow$ (Active)

- Advantages of prodrug over the active form
  - more stability,
  - better bioavailability
  - activated selectively at the site of action
  - less side effects and toxicity
Classification of biotransformation reaction

I. Nonsynthetic/Phase I/Functionalization reactions

- active or inactive metabolite

• 5 types
  - Oxidation
  - Reduction
  - Hydrolysis
  - Cyclization
  - Decyclization
II. Synthetic/Conjugation/ Phase II reaction

Mostly inactive \(\rightarrow\) metabolite

- VII Types:
  - (i) Glucuronide conjugation
  - (ii) Acetylation
  - (iii) Methylation
  - (iv) Sulfate conjugation
  - (v) Glycine conjugation
  - (vi) Glutathione conjugation
  - (vii) Ribonucleoside/nucleotide synthesis
Nonsynthetic reactions

(i) Oxidation: This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical.

- Eg. Barbiturates, phenothiazines, imipramine, ibuprofen, paracetamol
(ii) Reduction: This reaction is the converse of oxidation

- Involves cytochrome P-450 enzymes working in the opposite direction.

- Eg. Chloralhydrate, chloramphenicol, halothane, warfarin.
(iii) **Hydrolysis** This is cleavage of drug molecule by taking up a molecule of water.

\[
\text{Ester} + \text{H}_2\text{O} \xrightarrow{\text{esterase}} \text{Acid} + \text{Alcohol}
\]

Hydrolysis occurs in liver, intestines, plasma and other tissues.

• Eg: Procaine, lidocaine, procainamide, aspirin.
(iv) **Cyclization:** This is the formation of ring structure from a straight chain compound e.g. Proguanil.

- **Proguanil**
  - ![Proguanil Structure](image)

- **Cycloguanil**
  - ![Cycloguanil Structure](image)

- **PS-15**
  - ![PS-15 Structure](image)

- **WR99210**
  - ![WR99210 Structure](image)

- **JPC-2056**
  - ![JPC-2056 Structure](image)

- **JPC-2067**
  - ![JPC-2067 Structure](image)
(v) **Decyclization**: This is opening up of ring structure of the cyclic drug molecule e.g. Barbiturates, phenytoin.
Phase II: Synthetic reactions

- These involve conjugation of the drug or its phase I metabolite with an endogenous substrate to form a polar highly ionized organic acid which is easily excreted in urine or bile.
1. **Glucuronide conjugation**

- This is the most important synthetic reaction carried out by a group of UDP-glucuronosyl transferases (UGTs).

- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose.

- Eg. chloramphenicol, aspirin, paracetamol, morphine, metronidazole.
Hydroxyl or carboxylic acid group + glucuronic acid

UGTs  Conjugation

Increase molecular wt

Excreted in bile

Reabsorb in intestine

Enterohepatic circulation  Prolong action
(ii) Acetylation

- Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A e.g. sulfonamides, isoniazid.

- It shows genetic polymorphism (slow and fast acetylators).
(iii) Methylation

- The amines and phenols group of drugs can be methylated.

- Methionine and cysteine acting as methyl donors e.g. histamine.
(iv) Sulfate conjugation

- The **phenolic compounds and steroids** are sulfated by **sulfotransferases (SULTs)**

- e.g. chloramphenicol, sex steroids
(v) Glycine conjugation

- Salicylates and other drugs having carboxylic acid group are conjugated with glycine,

- It is not a major pathway of metabolism.
(vi) Glutathione conjugation

- Highly reactive quinone or epoxide intermediates conjugate with glutathione mercapturate.

- It serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs e.g. paracetamol
Acetaminophen

- Glucuronide moiety (Non-toxic)
- Sulfate moiety (Non-toxic)

P450 (2E1)

N-acetyl-p-benzo-quinone imine (NAPQI) (TOXIC)

- Glutathione
  - Cysteine and mercapturic acid conjugates (non-toxic)

- NAC
A large amount of quinine or epoxide intermediate

Glutathione supply falls short

Formation of toxic adducts with tissue constituents

Tissue damage.
(vii) Ribonucleoside/nucleotide synthesis

- This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.
Simultaneous or sequential metabolism of drugs
Drug Metabolizing Enzymes

- Microsomal enzymes
- Non-microsomal enzymes
Microsomal enzymes

• **Location:** smooth endoplasmic reticulum, primarily in liver, also in *kidney, intestinal mucosa* and *lungs*.

• **Eg. of ME**
  - Monooxygenases,
  - cytochrome P 450,
  - glucuronyl transferase etc.
ME catalyse
- oxidations,
- reductions,
- hydrolysis
- and glucuronide conjugation

Microsomal enzymes are inducible by
- drugs
- diet.
Non microsomal enzymes

- **Location**: Cytoplasm, mitochondria of Liver & Plasma.

Eg of NME
- Flavoprotein oxidases,
- esterases,
- amidase
- And conjugases.
• Reaction catalysed are:
  • Some oxidations and reductions,
  • many hydrolytic reactions
  • and all conjugations except: glucuronidation.

• The **nonmicrosomal enzymes** are
  - not inducible
  - but many show *genetic polymorphism*. 
• Both microsomal and nonmicrosomal enzymes are deficient in the newborn

more susceptible to many drugs e.g. chloramphenicol, opioids.

Low dose of drug used usual dose prod toxicity
INHIBITION OF DRUG METABOLISM

• 2 types
  1. Competitive enzyme inhibition
  2. Non-competitive enzyme inhibition

• One drug can **competitively inhibit metabolism of another** if it utilizes the same enzyme or cofactors.

• Occurs in a **dose related manner** and can **precipitate toxicity of the object drug**.
- Metabolism of drugs with high hepatic extraction is dependent on liver blood flow.

- eg. Propranolol decreases hepatic blood flow.

  Reduces rate of lidocaine metabolism
MICROSOMAL ENZYME INDUCTION

Many drugs, insecticides and carcinogens interact with DNA

Increase the synthesis of microsomal enzyme protein (cytochrome P-450 and glucuronyl transferase).

Increases rate of metabolism.
• Eg. Phenobarbiton - inducers of Cyp3A and Cyp2D6

Increase the rate of metabolism by 2-4 fold.
Polycyclic hydrocarbons like 3-methyl cholangrene and benzopyrene found in cigarette smoke, charcoal boiled meat, and industrial pollutants induce CYP1A isoenzymes.
Other **important enzyme inducers** are:

- Chloral hydrate,
- phenylbutazone,
- griseofulvin.
Consequences of microsomal enzyme induction

1. Decrease **intensity or duration of action** of drugs that are inactivated by metabolism.
   
   Eg. Oral contraceptives

2. Increase **intensity of action of drugs** that are activated by metabolism.

   Eg. Acute paracetamol toxicity
3. **Tolerance**: In case of autoinduction.

Eg. Carbamazapine.

4. **Precipitation of acute intermittent porphyria**-disease in which an **important part of hemoglobin, called heme**, is not made properly.

5. Interfere with **adjustment of dose** of another drug.
6. Interfere with **chronic toxicity testing** in animal.

7. It affect metabolism of other drugs eg.

1. Phenytoin
2. Warfarine
3. oral contraceptive
4. chloramphenicol etc.
Summary

- Decrease the intensity
- Increases intensity of drug
- Tolerance
- Prophyria
- Interfere with adjustment of dose
- Interfere with chronic toxicity testing
FIRST PASS (PRESYSTEMIC) METABOLISM

• Definition:

Metabolism of drug during its passage from site of absorption into systemic circulation.

1. Orally administered drug

Come in contact with intestinal & liver enzyme

Undergoes first pass metabolism
2. It is also occure in skin & lungs

lower magnitude
<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>Aspirin</td>
<td>Isoprenaline</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Quinidine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Desipramine</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Nortriptyline</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Chlorpromazine</td>
<td>not given orally</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Pentazocine</td>
<td>high oral dose</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alprenolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salbutamol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glyceryl trinitrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pethidine</td>
</tr>
</tbody>
</table>
Attributes of drugs with high first pass metabolism:

(a) **Higher oral dose** than sublingual or parenteral dose.

(b) **Marked individual variation** in the oral dose due to **differences in the extent of first pass metabolism**.
(c) Oral bioavailability is apparently increased in patients with severe liver disease.

(d) Oral bioavailability of a drug is increased if another drug competing with it for first pass metabolism (e.g. Chlorpromazine and propranolol).
Excretion of drug

- Drug can be excreted in their **unchanged form or as metabolites** by
  - Kidney
  - lungs
  - intestine

- And to lesser extend by the
  - sweat
  - salivary
  - and mammary glands.
• **More water soluble** a drug or metabolite

  More efficiently it is **eliminated from the body**.

• **Renal excretion:**

  3 major processes involve in the excretion of drugs by the **kidney**

  1. Glomerular filtration
  2. Tubular secretion
  3. Tubular reabsorption
• Glomerular filtration & Tubular secretion

  Remove the drug from plasma

• Tubular reabsorption

  Retain drug in plasma

• The net excretion of drug depends therefore on sum total of three processes.
Glomerular filtration

- By this process drug molecules diffuse out of the blood --- filtrating the glomeruli of the nephron -- passes into the tubuls of the kidney.

- Drug with molecular wt of 500 or less

  Unimpeded diffusion of the drug
Drug with mol wt 5000-69000

partially impeded diffusion.

Result:

- All the drug which are **not protein bound** appear in the glomerular filtrate.
• Glomerular filtrate - 120 L / day

• But daily urine volume - 1-2 % of this volume.

• **Factors influence renal excretion by glomerular filtration:**

1. **Molecular size** – small

   Faster/ More is excretion

2. **Plasma protein binding** – Less

3. **Renal flow and volume of filtrate** – More
Tubular secretion

- Proximal renal tubul - actively secrete certain drug and transporting them from the blood stream → the tubular fluid.

- Acidic drugs eg. salicylates & penicilline.

- Basic drugs eg. Adrenaline & noradrenaline.
• Many drugs which are secreted by tubuls are also filtered by the glomeruli

Having very short duration of action

• Eg Penicilline
How to overcome short duration of action of penicillin due to tubular secretion:

- Since tubular secretion required energy, it can be inhibited by certain drug.

- Eg. **Probenicide** is often combined with **penicillin**

  inhibit active secretion process of penicilline.

Prolonging the **duration of action** of penicilline
Tubular reabsorption

- **Location**: Almost throughout renal tubul.
- Reabsorption retained drug back into the blood.
- Similar to absorption from the gut wall.
- Drug molecule passively transported through tubular reabsorption.
Enhancing the excretion of drug in case of overdosing and poisoning

Drug existing in the **non ionized lipid soluble state**

completely reabsorbed

- **Weakly acidic drug** e.g. salicylate excreted better if PH become alkaline and vice versa.
• Acidification or alkalization of urine with drug like ascorbic acid or sodium bicarbonate used to hasten the excretion of drug in case of overdosing or poisoning.
Biliary excretion

- Minor rout of elimination for unmetabolized drug.
• Major route of elimination for metabolites eg. Water soluble conjugates like glucuronides.
Excreted in bile

Reabsorb in intestine

Excreed into Faces

Prolong the action of drug
Pulmonary excretion

• Important for gaseous and volatile liquid like general anesthetics.

• Blood stream  Alveolar membrane  Expired air
• **Breathometer** is often used to estimate the blood level of alcohol which correlate with degree of intoxication.
Excretion in sweat, saliva, milk and gastric juice

- Occur by **passive diffusion** of **non-ionized** form of drug.

- Some are **transported to suckling infant in breast milk**

  Drug used by **breast feeding** mother should be restricted to minimum.