

Drug metabolism

Pharmacology: It is the study of drug action. It can be divided into two areas:

Pharmacodynamics (how drugs work) and **Pharmacokinetics** (the fate of drugs in the body). **Pharmacodynamics** is what the drug does to the body, whereas **pharmacokinetics** is what the body does to the drug.

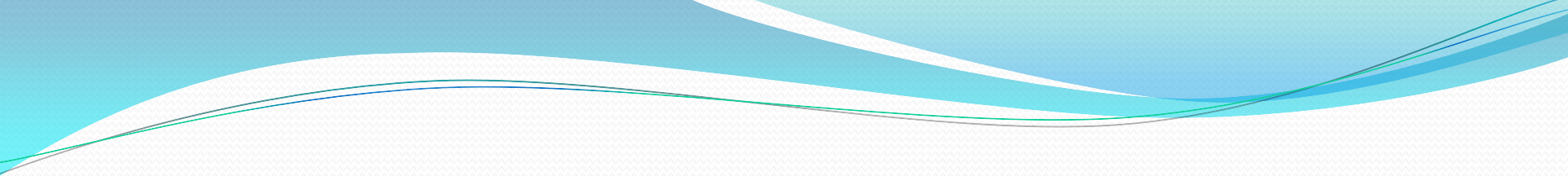
The pharmacological effects of a drug depend on its free concentration at its site of action; in other words the Pharmacodynamics of a drug depends on its pharmacokinetics.

Essentially pharmacokinetics covers the:

- **Absorption**
- **Distribution**
- **Metabolism**
- **Elimination**
- **Of a drug (abbreviated to ADME)**

Drug Metabolism

As soon as a drug enters the body it will begin to be metabolized. Most drugs are foreign to the body and could have toxic effects. So , drug metabolism is a process of “ **Deactivation and Elimination**” of a given drug. Most drugs are lipid-soluble and therefore it is inefficient to excrete them unchanged in aqueous urine via the kidneys.



The problem is that the **lipid-soluble** molecules are reabsorbed from the urine into the blood in the renal tubules. Typically only 1% of the total amount of drug in the body may be excreted in an unchanged state. Therefore drug molecules are altered during metabolism to make them more **water soluble**, so that the metabolites can be efficiently excreted via the urine.

The yield of drug metabolism

Active ----- **Inactive** (Most of cases).

Inactive (pro-drug)----- **active** (Few cases).

Active ----- **Active** (Few cases).

Types of drug metabolism reactions

Phase I Metabolism: It comprises 'Oxidation, Reduction and Hydrolysis'.

The process requires a complex enzyme system called the cytochrome P₄₅₀ (CYP) system and a high-energy cofactor = Nicotinamide Adenine Diphosphate (NADPH).

Some drugs already have a reactive group on their molecule, so they can bypass phase I and go straight into **phase II** metabolism. Example :
“Morphine”.

Phase II Metabolism: the reactive intermediate from phase I is conjugated with a polar molecule to form a water-soluble complex. The process is also known as **conjugation**.

Glucuronic acid is the most common conjugate, as it is a freely

available by-product of cell metabolism. Drugs can also be commonly conjugated with sulphate ions and glutathione. Phase II metabolism requires specific enzymes and a high-energy cofactor = **Uridine Diphosphate Glucuronic acid (UDPGA)**.

Sites of Metabolism

- **Liver** (the main site) (necessary enzymes)

Other sites:

- **Lungs.**
- **Kidneys.**
- **Gastrointestinal tract.**
- **Plasma.**

Variation in Drug Metabolism in the Population

1- Genetic Factors:

Individual variation lead to different rates of metabolism. drug effects can vary from person to person. There are about 50 different haem-containing enzymes the cytochrome P₄₅₀ system (CYP) and there are polymorphisms in the human population.

The isoform CYP₃ A₄ is the most important, accounting for about 55% of drug metabolism, Some individuals may lack the gene which codes for a crucial enzyme and this can have a large effect on drug metabolism.

Example :

- 1- Slow and fast acetylators.
- 2- Low levels of pseudocholinesterase enzymes in the plasma.

2- Environmental Influences:

Exogenous factors !!!!!

Example : Enzyme inhibition or induction.

Pesticides , Ethanol, nicotine and barbiturates are well known enzyme inducers.

Erythromycin , Chloramphenicol and Metronidazole are liver enzymes inhibitors.

3- **First pass effect: (Enteric rout)**

Substances absorbed from the lumen of the ileum via (venous blood) to hepatic portal vein and is transported directly to the liver.

Liver is the main site of metabolism. Large portion of drug will be metabolized. So , a small portion will reach systemic circulation.

Example : 1 gram of oral paracetamol tablet , only 10% reaches the blood.

Example of drug metabolism: metabolism of alcohol

Metabolic response to alcohol:

Most of the alcohol (>90%) that enters the body is metabolized, the remainder (<10%) being excreted passively in the urine and on the breath. The major site of alcohol metabolism in the body is the liver.

Most of the alcohol is oxidized by **alcohol dehydrogenase** (a low specificity enzyme) to acetaldehyde and this is further oxidised to acetate by **aldehyde dehydrogenase**. The acetate is converted to acetyl-coA.

Acetaldehyde is extremely toxic to cells and its toxicity is normally kept to a minimum because aldehyde dehydrogenase has a very low K_m for acetaldehyde (10 $\mu\text{mol/L}$) and removes it as soon as it is formed.

However, when the consumption of alcohol is prolonged and excessive, sufficient **acetaldehyde** can accumulate to cause liver damage. In addition, the decrease in the **NAD⁺/NADH** ratio and the increased availability of acetyl-coA, as a result of alcohol catabolism, have significant effects on liver metabolism.

Effects of decrease in NAD^+/NADH ratio on liver cell metabolism

The increased levels of **NADH** in the liver caused by alcohol oxidation means that **NAD⁺** levels are inadequate for fatty acid oxidation, conversion of lactate to pyruvate and metabolism of glycerol. The decreased utilization of lactate by liver cells leads to its accumulation in the blood and may cause lactic acidosis.

Increased levels of **lactate** decrease the ability of kidney to excrete **uric acid** and crystals of urate may accumulate in tissues producing the painful condition of **gout**. The low **NAD⁺** level combined with the inability of the liver cells to use lactate and glycerol means that **gluconeogenesis** cannot be activated and fasting hypoglycemia may become a serious problem. The poor dietary habits of the alcoholic may also contribute to the **hypoglycemia** as liver glycogen levels tend to be low.

Effects of increased availability of acetyl-coA

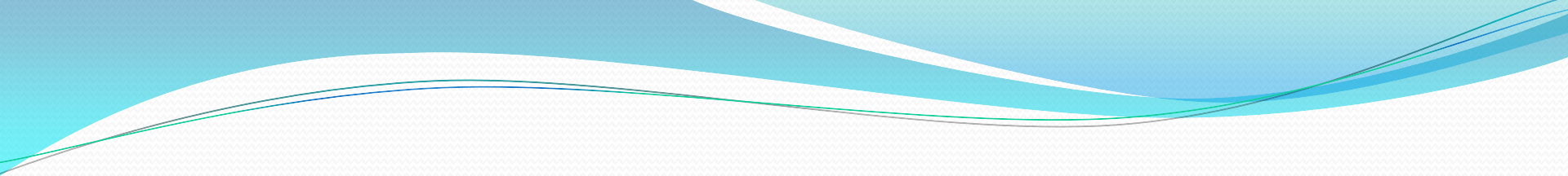
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The increased availability of **acetyl-coA** to liver cells, at a time when it cannot be oxidized because of the low **NAD⁺/NADH** ratio, leads to increased synthesis of fatty acids and ketone bodies. The newly synthesized **fatty acids** are converted to **triacylglycerols**. These cannot be transported from the liver cells because of the lack of **lipoprotein** synthesis and they therefore contribute to the **fatty liver**. In some cases, the production of ketone bodies is sufficient to cause **keto-acidosis**.

Effects of damage to liver cells caused by toxic effects of acetaldehyde

- Damaged liver cells have **leaky plasma membranes** that result in the loss of enzymes from the cells. These enzymes include *transaminases and gamma glutamyl transpeptidase* and their appearance in the blood is used diagnostically as an indicator of **liver cell damage = (abnormal liver function tests)**.
- Failure of liver to conjugate **bilirubin = hyperbilirubinemia = jaundice = yellowish discoloration of skin and sclera.**

- Decreased liver capacity to synthesize urea from ammonia = **hyperammonaemia** and increased levels of **glutamine**.
- Reduced protein synthesis in liver leads to decreased synthesis of **albumin**, **clotting factors** and **lipoproteins**.
- Low serum albumin = **Oedema**.
- Low serum clotting factors level = ↑ **clotting time**.



- Failure to synthesize lipoprotein = **Fatty liver.**

Indirect effects of excessive alcohol consumption

The cost of alcoholic beverages and their effects on the central nervous system are such that excessive consumption is associated with poor dietary habit. There are likely to be vitamin and mineral deficiencies and there may also be inadequate protein and carbohydrate intake.

Direct effect of alcohol on gastrointestinal tract

Direct damage to GIT lining cells:

- **Loss of appetite.**
- **Diarrhea.**
- **Impaired absorption of vitamin K, folic acid, pyridoxine and thiamine = Bleeding tendency , anaemia and Wernicke-Korsakoff syndrome with mental confusion and unsteady gait.**

Treatment of Alcohol Dependence

By using **Disulfiram** = Inhibitor of the aldehyde dehydrogenase enzyme.

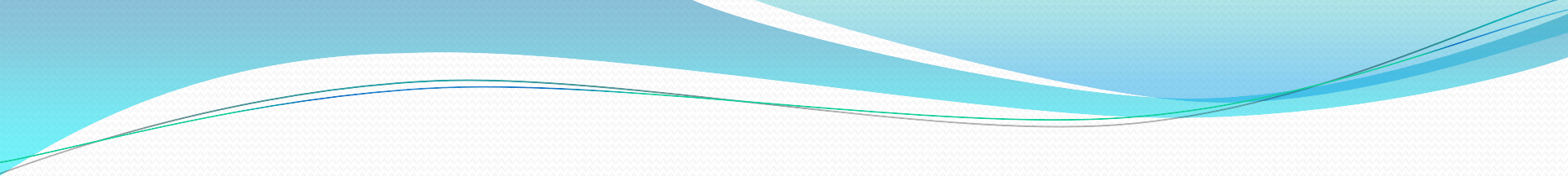
If the patient drinks alcohol then acetaldehyde will accumulate in the blood causing nausea and flushing which aid in treating alcohol dependence.

Metabolism of Paracetamol

Paracetamol is a widely available antipyretic and analgesic drug.

Paracetamol is metabolised by **phase II** conjugation with **glucuronide** or **sulphate**.

If a toxic dose is ingested then these pathways become quickly saturated. Under these conditions paracetamol undergoes **phase I** metabolism, producing a toxic metabolite, **N-acetyl-p- benzoquinone imine (NAPQI)**.



This metabolite is itself toxic to hepatocytes, but it also undergoes **phase II** conjugation with **glutathione**, so it depletes the cells of glutathione, which is an important antioxidant. This causes destruction of liver cells and liver failure occurs over a period of several days.

The most appropriate questions

A-The objective of drug metabolism is to :

- 1- To increase drug activity.
- 2- To lengthen drug half life.
- 3- To convert a drug to non-toxic one.
- 4- To covert lipid soluble drug to water soluble one that can be excreted in urine.

B-Regarding drug metabolism reactions :

- 1- Phase I reaction is mandatory for all drugs to pass through it.
- 2- In phase II reaction , drug molecule undergo oxidation , reduction or hydrolysis.
- 3- Phase I comprises addition of functional group to drug molecule.
- 4- Phase I reaction utilize cytochrome P₄₅₀ (CYP) enzyme system.

C- Factors affecting drug metabolism :

- 1- Different ethnic people show different rate of drug metabolism.
- 2- Erythromycin fasten warfarin metabolism.
- 3- Drug with pronounced 1st pass metabolism can achieve high blood concentration.
- 4- Rectal route of drug administration is 100% free of 1st pass of metabolism.



D- Concerning with excessive alcohol metabolism :

1- It results in low **NAD⁺/NADH** ratio .

2- It stimulates the aerobic glycolysis inside liver cells.

3- It precipitates gouty arthritis.

4- It increases blood PH.



E- Consequences of Excessive alcohol metabolism :

1- Hypoglycemia.

2- Hyperlipoproteinemia.

3- Hypercoagulability.

4- Hypouricemia.