

# **ACUTE & CHRONIC ETHANOL EFFECTS – An Overview**

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## Sites and rate of absorption of ethanol

- Absorption of ethanol starts in Oral mucosa and continues in Stomach and Intestine,
- High and low conc. of ethanol are absorbed slowly;
- Co-ingestion of food reduces rate of ethanol absorption,
- Blood conc. of ethanol peaks 30 - 60 mins after ingestion
- Liver metabolises over 90% of alcohol absorbed, thus the damaging effect that prolonged high intake has on liver,
- Kidneys, sweat, breath excrete 5 - 8% ethanol consumed;
- Rate of alcohol metabolism varies among individuals; higher in chronic alcoholics with facilitated liver enzymes (until their liver fails),

## What are some of the effects of Ethanol Metabolism?

- Moderate to excessive intake of ethanol severely affect the metabolic system,
- Metabolism of ethanol generates high amounts of reducing equivalents ( $\text{NADH} + \text{H}^+$ ) in liver, which ultimately changes the Red-Ox state in liver (**Fig. 1**);
- Rate of ethanol metabolism is dependent on the capacity of the liver to re-oxidize these reducing equivalents, i.e.,
  - To convert  **$\text{NADH} + \text{H}^+$  to  $\text{NAD}$**

- If the capacity of the liver to carry out this function is affected, then a number of metabolic disturbances may arise, such as:
  - Hypoglycaemia,
  - Lactic Acidosis,
  - Ketoacidosis,
  - Hyperuricemia,
  - Fatty liver,
- Alterations in the metabolism of:
  - Galactose,
  - Corticosteroids,
  - Serotonin, and a number of other biological active amines

- Ethanol metabolism promotes a reduced intracellular state that interferes with Carbohydrate, Lipids and other aspects of Intermediary metabolism,
- Oxidation of ethanol is coupled with reduction of:
  - Pyruvate to Lactate,
    - It may cause hypoglycaemia and acidosis
  - Oxaloacetate to Malate,
- This may explain:
  - Reduced activity of Citric acid cycle (TCA cycle),
  - Reduced Gluconeogenesis, and
  - Increased Fatty acid synthesis, associated with ethanol metabolism

- Gamma- Glycerophosphate increases after ethanol consumption, resulting high Glycerol;
  - It promotes increased Triglyceride synthesis and leads to Hyperlipidemia,
- Ethanol binds directly to Gamma-Amino-butyric Acid (GABA) receptor in CNS and causes sedative effects, similar to those of Benzodiazepines, which bind to the same GABA receptor,
- Ethanol has direct effects on Cardiac Muscle, Thyroid tissue, and Hepatic tissue,

## What are some effects of ethanol on infants and toddlers?

- In young children, ethanol causes hypoglycaemia and seizures; it does not occur easily in older patients,
- Hypoglycaemia occurs because ethanol effectively inhibits Gluconeogenesis, which is vital in young children,
  - Glycogen stored in liver of young children is very low
- In toddlers who have not eaten for several hours, small quantities of ethanol can cause hypoglycaemia

## What is the effect of ethanol on Endoplasmic Reticulum?

- Endoplasmic Reticulum (Microsomes) plays major role in metabolism of foreign substances in cells (Xenobiotics),
- Hepatic Microsomal Enzyme Systems (Microsome Ethanol Oxidizing Systems, **MEOS**) are responsible for inactivation (detoxification) of drugs and chemicals,
- Some alcoholics frequently take Barbiturates & Tranquillisers, among other drugs,
  - Chronic ingestion of either alcohol or these drugs causes proliferation of Smooth Endoplasmic Reticulum causing increase in activity of the Microsomal enzymes,

- Increased activity of the Microsomal enzymes in chronic alcoholics results in faster inactivation of therapeutic drugs when the individual has not consumed alcohol,
- Example:
  - Anaesthesia of sober chronic alcoholic individual requires larger doses of the drug than casual drinkers,
  - However, when the alcoholic is burdened with alcohol, metabolism of the alcohol takes precedence over metabolism of sedative and tranquilizers.

- Alcohol consumption can affect the effectiveness of medications by accelerating the elimination of some (e.g., Barbiturates) and enhancing the toxicity of others (e.g., Acetaminophen),
- In chronic alcoholics, the rate of alcohol metabolism is increased because of activation of the MEOS (CYP2E1) enzyme system,
- MEOS is responsible for converting some analgesic drugs (Pain killers, such as Acetaminophen), into chemicals that are highly toxic to the liver;

## ACUTE ALCOHOL POISONING

- Effects of ethanol excess can be separated into two categories
- Those that are:
  - Directly related to blood alcohol level, e.g. Coma,
  - Caused by metabolic effects of regular high ethanol levels,
- Determination of blood alcohol concentration (BAC) is the best guide in both cases,
- If BAC cannot be estimated, then plasma Osmolality Measurement and Calculation of Osmolal Gap is used

$$\mathbf{OG = MO - CO}$$

{CO = Calculated Osmolality, MO = Measured Osmolality}

## TAKE NOTE

- Ethanol causes Elevated OG, but does not cause Anion Gap Acidosis,
- Methanol and Ethylene Glycol consumption causes elevated OG and Anion Gap Acidosis;
- Recovery from acute ethanol poisoning is usually rapid in the absence of renal or hepatic failure; it is speeded up if hepatic blood flow and Oxygenation is maximized;
- Rate of elimination of ethanol depends on several factors, and is dose dependent; Examples:
- For average adult, with BAC of 100mmol/l, rate of elimination is around 10 – 15mmol/hour;

# CHRONIC ALCOHOL ABUSE

## What are some of effects of chronic alcohol abuse?

- Alcohol is metabolised mainly by the liver, thus effects of chronic alcohol abuse may be due to either Toxicity of Acetaldehyde and/or failure of one or more of the many homeostatic and synthetic mechanisms in the liver;
- Hepatomegaly may be one of the early signs of chronic alcohol abuse,
  - It may be cause by accumulation of Triglyceride from Carbohydrate load and reduced Protein synthesis;

- Alcohol damages the lining of Small Intestine, decreasing absorption of several B Vitamins and Vitamin C,
- Thiamine deficiency is a particular concern with chronic alcohol consumption;
- Alcohol alters metabolism in the body: It causes
  - Impaired Glucose Tolerance and Diabetes Mellitus,
  - Increased blood concentration of Triglycerides,
  - Cirrhosis of the liver with resultant decreased blood albumin concentration,
  - Cardiomyopathy,
  - Coagulation defects,
  - Peripheral Neuropathy,
  - Hypertension, etc

## What are the effects of chronic alcohol abuse on liver?

- Chronic alcohol consumption affects the liver;
- Alcoholic liver disease progresses in phases:
  - **First phase is Fatty Liver**, because alcohol consumption increases synthesis and deposition of fat in the liver;
  - **Second phase is Alcoholic Hepatitis**: Inflammation of liver;
- Both phases are reversible if alcohol intake stops and adequate nutritional and health practices are followed;
- If alcohol consumption continues, Cirrhosis may develop resulting loss of functioning liver cells and accumulation of fibrous connective tissues;
- Chronic alcohol intake may also cause Hypertension, Heart disease, and Stroke;

# LABORATORY INVESTIGATIONS

**Serum glucose level:** Check if patient is hypoglycemic;

**Serum Electrolytes:**

- Determine the Anion gap,
- Acute ethanol intoxication usually does not cause significant Anion Gap metabolic acidosis,
- Presence of large Anion Gap or severe Acidosis may suggest the ingestion of Methanol or Ethylene Glycol;
- Patients with multiple-trauma can also have marked metabolic acidosis, and ethanol intoxication predisposes patients to trauma

## **Blood Alcohol Concentration (BAC):**

- BAC should be determined to obtain a starting level,
- Ethanol is metabolised at a fixed rate, thus duration of the effects of alcohol intoxication can be predicted;
- NOTE: Instead of enzymatic methods that use Alcohol Dehydrogenase, Gas Chromatography (if available) should be used to measure the BAC, because the Enzymatic methods do not distinguish between ethanol and other alcohols, such as Methanol and Isopropanol;

## Interpretation of BAC results

- Most laboratories have standards for interpreting their results, in relation with the clinical observation
- One way of interpreting the BAC results is as follows:
  - **Intoxication or Inebriation: 100 – 150 mg/dL;**
  - **Loss of muscle coordination: 150 – 200 mg/dL;**
  - **Decreased level of consciousness: 200 – 300 mg/dL;**
  - **Possibility of death: 300 – 500 mg/dL.**

## **Methanol level:**

- This result can be helpful if an ingestion of combined substances is suspected;
- Positive Methanol level can alert the Physician to a co-ingestion;

## Arterial blood gas level:

- Determination of the pH is important when poly-substance ingestion or Ketoacidosis is suspected,
- The  $p\text{CO}_2$  is helpful in assessing respiratory depression
- The pH can help in ruling out co-ingestion of methanol and ethylene glycol, because significant acedemia is associated with those ingestions;
- In most cases the co-ingestion of ethanol and methanol does not cause significant acidosis;

## **Serum Osmolality:**

- OG can provide information about the ethanol level in blood;
- $OG = \text{Measured Osmolality (MO)} - \text{Calculated Osmolality (CO)}$
- Normal OG is less than 10 mOsm/kg
- OG between 22 – 25 mOsm/kg is responsible for every 100 mg/dL of ethanol in Serum;
- In some cases concentration of ethanol (Et) consumed can be calculated using the equation:

$$\mathbf{Et = \{OG - 10\} \times 4.6}$$

- (4.6 is a derived factor used for this purpose)

## Effects of some compounds in reducing blood ethanol level

- Administration of Insulin, Glucose, Caffeine do not increase ethanol metabolism or alleviate CNS depression
- Glucose administration is important in patients who are hypoglycaemic as a result of ethanol intoxication, but this treatment does not clear ethanol from the blood;
- Fructose infusion can increase the metabolism and clearance of ethanol by about 25%;
- Use of Fructose is not recommended, because Fructose infusion can cause Lactic Acidosis, Severe Osmotic Diuresis and Gastrointestinal Symptoms;

- Vitamin and Electrolyte replacement is recommended for specific deficits detected by laboratory results;
- Thiamine replacement is an exception because it is the only vitamin for which routine administration is recommended, and it has been proved useful in patients with chronic alcohol abuse;
- Thiamine is given to prevent Wernicke syndrome;

## Diagnosis of Chronic Alcohol Abuse

- Currently no highly sensitive and specific Biochemical markers are available for diagnosis of alcohol abuse;
- Most common components used are:
  - Hyperuricaemia,
  - Elevated Gamma Glutamyl Transferase (GGT), which is increased in about 80% of alcohol abusers,
    - GGT is not a specific indicator because it is also increased in some liver diseases and it is induced by drugs such as Phenytoin and Phenobarbitone;
  - Elevated serum Triglyceride;