UNIVERSITY OF PNG
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
Discipline of Biochemistry and Molecular Biology

PBL SEMINAR
ACUTE & CHRONIC ETHANOL EFFECTS – An Overview

Sites and rate of absorption of ethanol

- Absorption of ethanol starts in Oral mucosa and continues in Stomach and Intestine
- High and low concentrations of ethanol are absorbed slowly;
- Co-ingestion of food also slows absorption of ethanol
- Concentration of ethanol peaks 30 - 60 minutes after ingestion
- Liver metabolises over 90% of alcohol absorbed resulting in damaging effect that prolonged high intake has on liver
- 5 - 8% of alcohol is excreted unchanged by the kidneys, sweat and breath
- Rate of alcohol elimination from blood stream varies between different individuals, especially chronic alcoholics who have facilitated liver enzymes (until their liver fails), so that they can metabolise alcohol at an abnormally high rate.

What are some of the effects of Ethanol Metabolism?

- Moderate to excessive intake of ethanol can severely affect the metabolic system
- Metabolism of ethanol generates an excess of reducing equivalents ($NADH + H^+$) in the liver, which ultimately changes the Redox state in the liver (**Fig. 1**)
- Rate of ethanol metabolism is dependent on the capacity of the liver to re-oxidize these reducing equivalents (to convert $NADH + H^+$ back to NAD)
- If the capacity of the liver to carry out this function is affected, then a number of metabolic disturbances may arise, such as:
    - Hypoglycemia, Lactic Acidosis, Ketoacidosis, Hyper-uricemia, Fatty liver, and 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, which promotes hypoglycemia and acidosis
    - Oxaloacetic acid 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.
    - Glycerol thus produced, promotes increased Triglyceride synthesis and leads to Hyperlipidemia

- Ethanol binds directly to the Gamma-Amino-butyric Acid (GABA) receptor in the 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 of the effects of ethanol on infants and toddlers?

- In young children, ethanol causes hypoglycemia and seizures these are not observed as often in older patients.
- Hypoglycemia occurs because ethanol effectively inhibits Gluconeogenesis, which is vital in young children, because their Glycogen store in the liver is very low.
- In toddlers who have not eaten for several hours, even small quantities of ethanol can cause hypoglycemia.

What is the effect of ethanol on the Endoplasmic Reticulum?

- Endoplasmic reticulum (Microsomes) is involved in the metabolism of substances foreign to the cells (Xenobiotics)
- Hepatic Microsomal enzyme systems (Microsome Ethanol Oxidizing Systems, MEOS) are responsible for the inactivation (detoxification) of many drugs and chemicals
- Some alcoholics frequently take Barbiturates and Tranquillisers, among other drugs
- Chronic ingestion of either alcohol or these drugs causes proliferation of the Smooth Endoplasmic Reticulum causing increase in the activity of the Microsomal enzymes
- Increased activity of the Microsomal enzymes in chronic alcoholics results in a faster inactivation of drugs when the individual has not consumed any alcohol, example
    - Anaesthesia of sober chronic alcoholic individual requires larger doses of the drug than casual drinkers
- On the other hand, when the alcoholic is burdened with alcohol, the 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 (such as Barbiturates) and enhancing the toxicity of others (such as Acetaminophen)
- In chronic alcohol drinkers, the rate of alcohol metabolism is increased because of the activation of the MEOS (CYP2E1) enzyme system.
- This enzyme system 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 concentration at the time, such as coma
    - Caused by the metabolic effects of continued high ethanol concentration

- Determination of blood alcohol concentration (BAC) is the best guide in both cases
- If BAC cannot be estimated, then plasma Osmolality (osmolarity) measurement and calculation of Osmolal gap can be used
    - Osmolal gap (Serum) = Measured osmolality – Calculated osmolality

Take Note:

- Ethanol can cause Elevated Osmolal Gap, but usually does not cause an Anion Gap Acidosis.
- Methanol and Ethylene Glycol consumption causes elevated Osmolal Gap and Anion Gap Acidosis

- Recovery from acute ethanol poisoning is usually rapid in the absence of renal or hepatic failure, and is speeded up if hepatic blood flow and Oxygenation is maximized.
- Rate of elimination of ethanol depends on a number of factors, and it is dose dependent.
- For example:
  - In an average adult, if the BAC is about 100mmol/l, the rate of elimination is around 10 – 15mmol/hour

CHRONIC ALCOHOL ABUSE:

What are some of the 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.
- Hepatomegaly may be cause by accumulation of Triglyceride synthesized from Carbohydrate load and reduced Protein synthesis
- Alcohol damages the lining of the Small Intestine, decreasing the absorption of several B Vitamins and Vitamin C.
- Thiamin deficiency is a particular concern with chronic alcohol consumption.
- Alcohol can alter storage, metabolism and excretion of vitamins and minerals
- Impaired Glucose Tolerance and Diabetes Mellitus,
- Increased blood concentration of Triglycerides,
- Cirrhosis of the liver with resultant decreased serum albumin concentration,
- Cardiomyopathy, Coagulation defects, Peripheral Neuropathy, Hypertension, etc

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

- Most significant physiological effects of chronic alcohol consumption occur in the liver
- Alcoholic liver disease progresses in a number of phases:
  - First phase is Fatty Liver, which occurs because alcohol consumption increases the synthesis and deposition of fat in the liver
  - Second phase, Alcoholic Hepatitis is an inflammation of the liver
    - Both of these conditions are reversible if alcohol consumption is stopped and good nutritional and health practices are followed
  - If alcohol consumption continues, Cirrhosis may develop
  - Cirrhosis is a chronic liver disease characterized by the loss of functioning liver cells and the accumulation of fibrous connective tissue.
  - The liver becomes fat and the tissue is replaced by inactive fibrous scar tissue
- In addition to causing liver disease, heavy drinking is associated with Hypertension, Heart disease, and Stroke

LABORATORY INVESTIGATIONS:

Serum glucose level:

- A bedside glucose finger stick with a Dextrostick is a quick and inexpensive method of assessing hypoglycemia

Serum Electrolytes:

- Anion gap should be determined.
- Acute ethanol intoxication usually does not cause significant Anion Gap metabolic acidosis.
- Presence of a large Anion Gap or severe Acidosis should suggest the ingestion of another substance, such as Methanol or Ethylene Glycol.
- Patients with multiple-trauma can also have marked metabolic acidosis, and ethanol intoxication predisposes patients to trauma

Serum Ethanol level:

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

Interpretation of the serum ethanol level results:

- Most laboratories have standards for interpreting their results, in relation with the clinical observation.
- One way of interpreting the 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; and
    - 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 pCO_2 can be helpful in assessing respiratory depression.
- The pH can help in ruling out the co-ingestion of methanol and ethylene glycol, because significant academia is associated with those ingestions.
- In most cases the co-ingestion of ethanol and methanol does not cause significant acidosis.

Serum Calcium and Magnesium levels:

- High concentrations of ethanol and its chronic use can deplete these cations.

Serum Osmolality:

- Osmolar gap can provide information about the ethanol concentration in the blood.
- Calculation of Osmolar gap:

Osmolar Gap (OG) = Measured Osmolality (MO) – Calculated Osmolality (CO).

Normal OG is less that 10 mOsm/kg.

[Note that an OG of between 22 – 25 mOsm/kg is responsible for every 100 mg/dL of ethanol in the serum].

- In most cases it is possible to calculate the concentration of ethanol (Et) consumed using the following equation:

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

(4.6 is a derived factor used for this purpose)

Effects of some compounds in reducing the ethanol level:

- Administration of Insulin, Glucose, Caffeine etc. do not increase ethanol metabolism or alleviate CNS depression.
- Glucose administration is important in patients who are hypoglycemic 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 only for specific deficits detected by means of laboratory testing.
- 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 there are no highly sensitive and specific Biochemical markers that can be use for the diagnosis of alcohol abuse.

The most common components used are:

- Hyperuricemia,
- Elevated Gamma Glutamyl Transferase (GGT).
    - This enzyme is increased in about 80% of alcohol abusers.
    - It is not a specific indicator as it is also increased in all forms of liver disease and is induced by drugs such as Phenytoin and Phenobarbitone.
- Elevated serum Triglyceride.