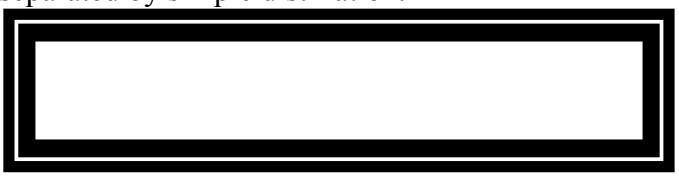
ALCOHOL

- Consumption of alcohol in one form or another is increasing all over the world, sometimes for its medical use but often for its pleasurable, stress relieving and blissful effects on the mind/mood.
- Alcohols are hydroxyl derivatives of aliphatic hydrocarbons.
- When unqualified, 'alcohol' refers to ethyl alcohol or ethanol.
- Pharmacology of alcohol is important for its presence in beverages and for alcohol intoxication, rather than a drug.

ETHYLALCOHOL (Ethanol):

- This is the main constituent of alcoholic beveranges and its obtained by fermentation of sugars by yeast.
- The alcohol is separated by simple distillation.



- It is a colourless, volatile and inflammable liquid.
- Neutral spirit contains 90-95% alcohol by volume.
- Wines containing more than 16% of alcohol are prepared by fortification with neutral spirit.
- The alcohol content of various beverages varies between 4-55 % by volume.
- Stronger preparations are called spirits.
- Beer contains 4-6% of alcohol.

MECHANISM OF ACTION:

- Alcohol has been believed to produce CNS depression by a generalised membrane action by altering the state of membrane lipids.
- However, recently specific effect on multiple receptor operated ion channels has been demonstrated at concentrations attained during moderate drinking.
- Alcohol promotes $GABA_A$ receptor mediated synaptic inhibition as well as inhibits NMDA and kainate receptors.
- Action of 5-HT on $5\text{-}HT_3$ inhibitory autoreceptor is augmented.
- Ethanol can directly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{++} channels.
- Blockade of adenosine uptake by alcohol could also contribute to synaptic depression.
- Turnover of NA in the brain is enhanced by alcohol through an opioid receptor dependent mechanism.
- This is probably important in the pleasurable effects of alcohol and genesis of alcohol dependence.
- Activity of membrane bound enzymes like Na^+ K^+ ATPase and adenylyl cyclase is also altered.
- The activity and translocation of channel/enzyme proteins in the membrane could be affected by alcohol through protein kinase C (PKC) and protein kinase A (PKA) mediated alteration in the state of their phosphorylation.

PHARMACOLOGICAL ACTION:

LOCAL ACTION:

- Applied locally, it evaporates quickly, has a cooling and refreshing effect, and is used for reducing the temperature in fevers.
- Eau-de-cologne and after-shave lotion are other example of cosmetic preparations used for their cooling effect.
- In conc of 40-50%, it has a rubificient and mild irritant action.
- Higher conc. Denature proteins by partial precipitation and dehydration; in such conc. It acts as an astringent and germicidal.
- Alcohol in the conc of 70% by wt acts as antiseptic; the action is seen only against vegetative forms of organisms;spores are resistant.

CENTRAL NERVOUS SYSTEM:

- Ethanol is primarily a CNS depressant and acts by enhancing the inhibitory $GABA_A$ receptor activity and inhibiting the excitatory NMDA receptors.
  (a) The pleasurable (euphoric) effects are mediated by a dopaminergic pathway that projects from the ventral tegmental area to the hypothalamic nucleus accumbens.
  (b) Long term exposure to alcohol brings about adaptive changes in the neuronal systems including downregulation of the inhibitory neuronal GABA receptors and upregulation of the excitatory glutaminergic receptors, thus increasing the central NA activity.
  (c) Sudden withdrawal of alcohol causes excitation and hyperactivity of the CNS.
- Alcohol diminishes process such as hesitation, caution and self-criticism.
- Initially, it produces euphoria, later, under its influence, mood swings and uncontrolled emotional out bursts are common.
- This initital effect is due to a depression of the reticular activitng system.
- The cortex is thus released from the integrating control or inhibitions required for purposeful activity.
- Alcohol reduces visual acuity and interferes with muscular co-ordination even in small doses.
- It impaires the ability of the brain to co-ordinate motor activity such as typing, standing, and hand steadiness.
- It is not an analgesic, it alters the patient's reaction to pain from one of concern to one of relative detachment.
- With increasing consumption, there occur difficulty in speech, unsteadiness of gait and complete loss of self control.
- Large quantities cause unconsciousness, respiration becomes slow, and the face become pale, the BP falls.
- Death occurs due to medullary depression, mainly the respiratory centre.

CARDIOVASCULAR SYSTEM:

- The effects are dependent on dose.
  - ✓ Small doses: produce only cutaneous (specially on the face) and gastric vasodilatation. Skin is warm and flushed and there may be conjunctival injection; BP is not affected.
  - ✓ Moderate doses: cause tachycardia and mild rise in BP due to increased muscular activity and sympathetic stimulation.

- ✓ Large doses: cause direct myocardial as well as vasomotor centre depression and there is fall in BP.
- Chronic alcoholism may contribute to hypertension and lead to cardiomyopathy.
- Atrial fibrillation and other cardiac arrhythmias may occur due to conduction defects and QT prolongation.

BLOOD:

- Regular intake of small to moderate amounts has been found to raise HDL levels and decrease LDL oxidation.
- This may be responsible for the 15-35% lower incidence of coronary artery disease in such individuals.
- Risk reduction greatest in high risk patients and protection is lost if more than 3 drinks are consumed.
- With chronic use megaloblastic anemia may occur.

BODY TEMPERATURE

- Alcohol is reputed to combat cold.
- It does produce sense of warmth due to cutaneous and gasric vasodilation, but heat loss is actually increased in cold surroundings.
- High doses depress temperature regulating centre.

RESPIRATION

- Brandy and whisky are reputed as respiratory stimulants in collapse.
- They irritate buccal and pharyngeal mucosa-may trasiently stimulate respiration reflexly.

GASTROINTESTINAL TRACT:

- Taken orally, it gives a local feeling of warmth and increase the salivary secretion probably by reflex action.
- It has an irritant action on the gastric mucousa and enjoys reputation as an appetizer.
- 50 ml of 7-10% alcohol increases the gastric secretion, by releasing histamine and gastrin from the gastric antrum, in addition to its psychic and local irritant effects.
- Conc. Above 15% inhibit both gastric motility and secretion.
- Conc. Above 20% reduce the enzymatic activity of the gastric and the intestinal juices.
- Conc of 40% and overhave a direct toxic effect on gastric mucosa and may precipitate gastritis, giving rise to pain, nauses, vomiting and other symptoms.

LIVER:

- Ethanol causes dose-related hepatotoxicity. The common effects are fatty infiltration and hepatomegaly.
- This results in:
  - ✓ Impaired gluconeogenesis
  - ✓ Glycogen depletion
  - ✓ Reduced synthesis of albumin and transferring
  - ✓ Diminished fatty acid oxidation
  - ✓ Increased synthesis of VLDL, with consequent hypertriglyceridemia

KIDNEY:

- Alcohol causes dieresis due to decreased tubular reabsorption of water following inhibition of ADH release.
- It increases the excretion of magnesium and calcium.

SKELETAL MUSCLE:

- It causes a decrease in muscle strength and irreversible damage to muscle tissue.

TETRATOGENIC EFFECTS:

- Drinking during pregnancy can cause fatal damage.
- The fetus has been described to have "characteristic facial appearance, microcephaly, growth retardation, mental deficiency and an increase in the frequency of major abnormalities"

SEX:

- Alcohol is reputed as an aphrodisiac. Aggressive sexual behavior is due to loss of restraint and inhibition.
- However, performance of the sexual act is often impaired.
- Chronic alcoholism can produce impotence, testicular atrophy, gynecomastia and infertility.

ENDOCRINE EFFECTS:

- Moderate amounts of alcohol increase adrenaline release which can cause hyperglycemia and other sympathetic effects.

PHARMACOKINETICS

ABSORPTION:

- Rate of alcohol absorption from stomach is dependent on its concentration, presence of food and other factors.
- Absorption from intestines is very fast. Thus, gastric emptying determines rate of absorption.
- Limited first pass metabolism occurs in stomach and liver.
- Its absorption from skin of adults is minimal but may be significant in infants.

Distribution:

- Alcohol gets distributed widely in the body, crosses blood brain barrier and placenta.

Metabolism:

- It is oxidised in liver to the extent of 98%.
- Alcohol $\xrightarrow{\text{alcohol dehydrogenase}}$ Acetaldehyde $\xrightarrow{\text{Aldehydedehydrogenase}}$ Acetate
- Metabolism of alcohol follows zero order kinetic.

Excretion:

- Occurs through kidney and lungs.

INTERACTIONS:

- Alcohol synergises with tranquilizers, antidepressents, antihistaminics, hypnotics, opioids-marked CNS depression.
- Sulphonylureas, some cephalosporins(cefoperazone, moxalactum, cefamandole) and metronidazole- disulfiram like effects.
- Tolbutamide and phenytoin metabolism.
- Hypoglycaemia by insulin and sulfonylureas is enhanced.
- Aspirin causes more gastric bleeding when taken with alcohol.
- Alcohoics are more prone to paracetamol toxicity due to enhanced generation of its toxic metabolite.

CONTRAINDICATIONS:

- Seldomly prescribed, but should be avoided by:
- Peptic ulcer, hyperacidity, gastroesophegal reflux patients.
- Epileptics.
- Severe liver disease patients.
- Unstable personalities

- Pregnant woman: moderate drinking-foetal alcohol syndrome- increased susceptibility to infections, intrautrine and postnatal growth abnormalities.
- On heavy drinking: miscarriage, stillbirths, low birth weight babies.

THERAPEUTIC USES:

- Antiseptic
- Rubifacient and counteriritant for sprains, joint pains.
- Rubbed on the skin to prevent bedsores.
- Antiperspirant and anti shave lotions.
- Alcoholic sponges to reduce body temperature
- Intractable neuralgias, severe cancer pain.
- To ward off cold
- Appetite stimulant and carminative
- Reflex stimulation in fainting/hysteria.

TOXICITY:

a. Side effects of moderate drinking:

- Nausea, Vomiting, Flushing, Hangover, Traffic accidents.

b. Acute alcoholic intoxication:

- Hypotension, Gastritis, Collapse, Respiratory depression, Coma and Death.

Treatment:

- ✓ Gastric lavage, maintain patent airway and take step to prevent aspiration of vomitus.
- ✓ Positive pressure respiration may be needed if it is markedly depressed.
- ✓ Most patients will recover with supportive treatment, maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion till alcohol is metabolised.

c. Chronic alcoholism:

- On chronic intake, tolerance develops to subjective and behavioural effects of alcohol.
- Physical dependence occurs only on heavy drinking and is associated with nutritional deficiency, because food is neglected and malabsorption may occur.
- In addition to impaired mental and physical performance, neurological affliction (polyneuritis, pellagra, tremors, seizers, loss of brain mass, wernicke;s encephalopathy and korsakoff's psychosis), alcoholic cirrhosis, hypertension, cardiomyopathy, CHF, arrhythmias, stroke and skeletal myopathy are other complication.

Withdrawal syndrome:

- Consists of anxiety, sweating, tremor, impairment of sleep, confusion, hallucination, delirium, convulsions and collapse.

Treatment:

- Psychological and medical supportive measures are needed during withdrawal.
- Many CNS depressants like barbiturates, phenothiazine, and chloral hydrate have been used as substitutive therapy, but benzodiazepines are the preferred drugs now.
- These have long duration of action.

ALDEHYDE DEHYDROGENASE INHIBITORAS:

DISULFIRAM:

- Therapy is initiated after ensuring that alcohol has not been consumed for at least 12 hrs.

- Treatment is initiated with 500 mg as a single daily dose for 1-2 weeks, followed by 125-250 mg OD as the maintenance dose; treatment may be continued for upto 1 year.
- After a week's therapy, even a small amount of alcohol produces toxic reaction, such as flushing, perspiration, palpitation, marked nausea, vomiting, fall of BP.
- The patient realizes that while on this drug he cannot tolerate even small amount of alcohol and abstains from drinking.
- Severe reactions can occur even with the first dose and hence, this treatment should be carried out in a hospital.

MECHANISM OF ACTION:

- The drug inhibits aldehyde dehydrogenase and blocks the oxidation of acetaldehyde.
- This raises the blood level of acetaldehyde which acts directly on the cardiovascular system.
- In addition, disulfiram also inhibits dopamine beta oxidation and thus interferes with the synthesis of NA which gets depleted.

ADVERSE REACTIONS:

- It can cause drowsiness, nauses, headache, cramps, fatiguability, a metallic taste in the mouth and acidosis.

DRUG INTERACTIONS:

- Disulfiram inhibits metabolic degradation of warfarin, theophylline, benzodiazepines, carbamazepine, tricyclic antidepressant and phenytoin.

CONTAINDICATIONS TO DISULFIRAM:

- Hepatic and circulatory diseases
- Uncontrolled diabetes mellitus
- In alcoholics with obvious personality changes

METYL ALCOHOL:

- It is added to rectified spirit to render it unfit for drinking. It is only of toxicological importance.
- Unscrupulus mixing of methylated spirit with alcoholic beverages or its inavertent ingestion results in methanol poisoning.
- It is metabolisd to formaldehyde and formic acid.
- It is also a CNS depressant, but less potent than ethanol.
- Toxicity of methanol is largely due to formic acid.
- Blood level of more than 50 mg/dl is associated with severe methanol poisoning.
- Even 15 ml methanol has caused blindness and at 30 ml, death.

MANEFESTATIONS:

- Vommiting, headache, epigastric pain, uneasiness, dyspnoea, bradycadia, hypotension, delirium, coma.
- Due to formic acid, *acidosis* occurs.
- The specific toxicity of formic acid is retinal damage.
- Blurring of vision, congestion of optic disc followed by blindness always precede death due to respiratory failure.

TREATMENT OF METHANOL POISONING:

- Keep the patient in a quiet dark room, protect the eyes from light.
- Gastric lavage with sodium bicarbonate, supportive measures to maintain ventillation and BP.
- Combat *acidosis* by Sod. Bicarbonate infusion.

- When hypokalemia, Pot. Chloride infusion.
- Ethanol 100 mg/dl in blood saturates alcohol dehydrogenase and retards methanol metabolism. This treatment should be long.
- Haemodialysis.
- Fomepizole: specific inhibitor of alcohol dehydrogenase
- Folate therapy: Calcium leucovorin injection retards blood formate level by enhancing metabolism.