


Alcohol Pharmacology

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Alcohol-1

- Is primarily in the form of ethyl alcohol (ethanol)
 - Is the most commonly abused drug in the world
 - In the US 75% of the adults drink alcohol regularly
 - 8–10% of the people in the US has an **alcohol-use disorder**
 - Individuals who continue to drink alcohol despite adverse consequences suffer from **alcohol abuse**
 - Individuals with **alcohol dependence** exhibit:
 - tolerance to alcohol
 - signs and symptoms upon withdrawal
 - demonstrate an inability to control their drinking
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Alcohol-2

- The medical costs of alcohol abuse are staggering:
 - 600,000 visits to the ER
 - 85,000 deaths/year in the US
 - Each year thousands of children are born with morphologic and functional defects
- Despite the investment in research, alcoholism remains a common chronic disease that is difficult to treat
- In addition to ethanol, methanol and ethylene glycol toxicity occurs frequently

Consumption Patterns

- Most frequently abused drug in North America and the world
- Consumed regularly by over one-half the adult population of Canada
- One million Canadians are alcoholics
- Per capita annual consumption of 10 L (2 drinks per day)

Ethanol – Uses

Local: antiseptic, antiperspirant and aftershave

Alcohol sponges – to reduce body temperature

Appetite stimulant and carminative: 30 – 60 ml of 7-10%

Neuralgias: severe cancer pain – injection round the nerve

As antidote for methanol Poisoning




Effects of alcohol consumption - Acute

▶ CNS:

- depressant – dose dependent manner

Plasma concentration	Expected effects
30 – 60 mg/dl	Anxiolytic, euphoria and excitation. Hesitation, self restraint, caution are lost Impaired coordination – mood and feelings are altered
80 -150 mg/dl	Mental clouding, ataxia, disorganization of thought and impairment of memory and drowsiness
150 – 200 mg/dl	Sloppy, ataxia and drunkenness - Slurring of speech, loss of judgment and inhibition
200 – 300 mg/dl	Stupor and unconsciousness

Mechanism:

- ▶ GABAA receptor mediated synaptic inhibition by chloride channel opening
 - ▶ Inhibition of NMDA (N-Methyl-D-Aspartate) excitatory amino acid receptor. Controls synaptic plasticity and memory function.
 - ▶ Stimulates 5-HT₃ (Inhibitory autoreceptors) receptors
 - ▶ Cerebral Nicotinic Cholinergic Receptors (Na channel)
 - ▶ Inhibits Voltage sensitive Neuronal Ca channels
 - ▶ Pleasure and alcohol dependence: DA, Endorphins
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Physiological Responses Consumption and Consequences

- Graded onset of disrupted motor function:
 - slight difficulty with balance
 - some ataxia
 - slurring of speech
- decrements in skilled processes requiring:
 - attention
 - evaluation
 - judgment and motor responses
 - decline in driving abilities
- decrements in reaction time to simple auditory or visual stimuli

Effects of alcohol consumption (acute)-1

- ▶ Impaired performance, slowing of reflexes
- ▶ Induces sleep – but not ideal hypnotic
- ▶ Analgesic – but not dependable
- ▶ Anticonvulsant action – but not ideal anticonvulsant as it decreases seizure threshold later

Effects of alcohol consumption (acute)-2

▶ CVS:

- Small doses – cutaneous vasodilatation, flushing
- Medium dose – tachycardia and mild rise in BP
- Large dose - Vasodilatation due to direct vascular smooth muscle dilatation and vasomotor center depression (clinical implication)

▶ Respiration:

- Stimulation of Respiration – by irritation of pharyngeal and buccal mucosa
- Central action – depression

▶ Blood:

- Moderate drinking increases HDL-cholesterol level
- Decrease in LDL oxidation

Effects of alcohol consumption (acute)-3

- GIT:
 - Dilute alcohol at low doses - stimulate GI secretion
 - Higher doses (>20%) inhibit GI secretion
 - Acute consumption – pylorospasm, gastritis, vomiting, reflux
 - Mallory-Weiss lesion
 - A/C pancreatitis

Effects of alcohol consumption – (acute) - 3

- Kidney: Diuresis – increased water ingestion and inhibition of ADH by alcohol
- Liver – Alcoholic Cirrhosis
- Uterus: Relaxation of uterine muscles

- Endocrine:
 - Low dose – Adrenaline release and hyperglycemia
 - High dose – Hypoglycemia – due to:
 - hepatic depletion of glycogen
 - inhibition of gluconeogenesis

Pharmacology Absorption and Distribution

- Water soluble, readily diffuses through any mucous membrane
- Quickly absorbed from stomach and small intestines
- Absorption affected by
 - delayed gastric emptying
 - concentration of alcohol in a drink
- Diffuses quickly from bloodstream into aqueous compartment of all tissues, body fluids and alveolar air
- Volume of distribution (V_d) = volume of total body water
- Alcohol in the alveolar space is proportional to that in pulmonary blood
- Breath/blood ratio incorporated into devices such as breathalyzers

Absorption

- Rapidly absorbed from small intestine, and colon but slowly from stomach
- First pass metabolism in stomach and liver
- Maximal blood concentration within 30 to 90 minutes
- Can be absorbed through the lungs
- Can be absorbed through skin



Distribution

- Uniformly distributed throughout tissues and body fluids
- $V_d - 0.7L/Kg$
- Readily crosses placenta
- Crosses BBB readily

Elimination

- Urinary Excretion
- Exhalation- 0.05% of blood conc. Is present in exhaled air
- Skin with sweat

Metabolism

- Up to 98% is Metabolized
- Main enzyme is hepatic alcohol dehydrogenase
- Also metabolized in small amounts by hepatic microsomal enzyme CYP2E1
- Rate is constant (not increased by concentrations in the blood) – zero order (8-12 ml/H of absolute alcohol)
- About 30 ml in 3 hours
- Concentration in exhaled air is 0.05% of blood concentration – used in medico legal purposes

Adverse Effects of Alcohol

▶ Acute Effects

- Nausea, Vomiting, hangover and traffic accidents
- CNS Depressant
- Depression of inhibitory control
- Vasodilatation, warm, flushed, reddish skin
- Emotional outbursts
- Decreased memory & concentration
- Poor judgment
- Decreased reflexes
- Decreased sexual response

Adverse Effects of Alcohol – contd.

▶ Acute Alcohol Intoxication:

- Estimated ED50: 150 mg/100 ml and LD50 = 500 mg/100ml
- Therapeutic index about 3.5
- Hypotension, hypoglycemia, respiratory depression coma and death
- Death due to respiratory depression or inhaled vomit

- Treatment:
 - Gastric lavage
 - Endotracheal intubations
 - Fluid and electrolyte balance
 - Glucose infusion
 - Thiamine injection 100 mg in 500 ml of glucose IV
 - Haemodialysis

Goals in the Treatment

- ▶ Prevent severe respiratory depression and aspiration of vomitus.
- ▶ The average blood alcohol concentration in fatal cases is above 400 mg/dL; However, the lethal dose of alcohol varies because of varying degrees of tolerance.
- ▶ Metabolic alterations may require treatment of hypoglycemia and ketosis by administration of glucose.
- ▶ Thiamine is given to protect against the Wernicke-Korsakoff syndrome.
- ▶ Alcoholic patients who are dehydrated and vomiting should also receive electrolyte solutions.
- ▶ If vomiting is severe, large amounts of potassium may be required as long as renal function is normal. Especially important is recognition of decreased serum concentrations of phosphate, which may be aggravated by glucose administration.

Toxic Effects - Chronic Alcoholism -1

▶ GIT:

- Gastritis and damage to the mucosa – **anemia**
- Intestinal damage: Lack of absorption - Deficiency of water soluble vitamins and amino acids
- Less or no food intake (enough calorie)
- Acute pancreatitis

▶ Liver cirrhosis – scarring of liver

- Usually fatal if drinking is not stopped
 - Fatty infiltration (excess in NADH)
 - Oxidative stress and cellular necrosis
 - Damage to hepatocytes and inflammation – aldehyde
 - Glutathione depletion
 - Microsomal enzyme induction

Chronic Alcoholism -2

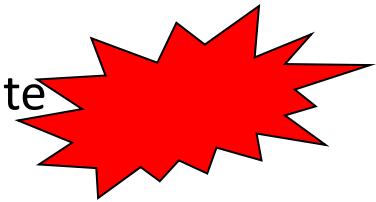
- **Neurological:** Polyneuritis, tremors, seizures, loss of brain mass, psychosis and encephalopathy
- **CVS:** Hypertension, cardiomyopathy, CHF arrhythmias and stroke
- **Reproduction**
 - Alcohol is a teratogen, it causes birth defects
 - Fetal Alcohol Syndrome or Alcohol-Related Birth Defects
 - Symptoms include retardation, poor coordination, loss of muscle tone, low birth weight, slow growth, malformation of internal organs and peculiar facial characteristics
- **Hormonal:** Impotence and infertility

Disulfiram (Antabuse)

- ▶ Internationally marketed as antabuse
- ▶ ALDH enzyme inhibitor
- ▶ **Alcohol + disulfiram** rise in concentration of aldehyde in blood and tissue distressing aldehyde syndrome
 - Symptoms: flushing, burning sensation, throbbing headache, perspiration, dizziness, vomiting, visual disturbance, mental confusion, fainting and circulatory collapse
- ▶ Uses: aversion technique in chronic alcoholics: only to motivated persons
 - Technique: abstain alcohol overnight and start with 1 gm on day 1 followed by 0.75 gm next day and 0.50 gm next day and so on. Effects start within few hrs of 1st dose and lasts for 2 weeks
 - Mechanism: irreversible inhibition of ALDH and synthesis of new enzyme takes time and thus person resolves not to drink for distressing symptoms
- ▶ Available as 250 mg tablets

Ethanol as Antidote

- ▶ Methanol, Ethylene glycol, Diethylene glycol
- ▶ Methanol poisoning – toxicological importance – unscrupulous mixing with alcoholic beverages
- ▶ Formic acid is toxic: above 50 mg/dl, lethal dose 75 – 100 ml, even 15 ml can cause blindness



- ▶ Methanol poisoning: vomiting, epigastric pain dyspnoea, bradycardia, acidosis – permanent retinal damage and Death
- ▶ Mechanism: Ethanol saturates *alcohol dehydrogenase* enzyme - no metabolism of Methanol to form Formic acid

Methanol Poisoning treatment

- ▶ Patient in dark room, Ventilation and BP supportive measures
- ▶ Gastric lavage with sodabcarb if brought immediately
- ▶ IV sodabcarb to combat acidosis – large quantity may be required
- ▶ Ethanol 10% in water – nasogastric tube with loading dose of 0.7 ml/kg followed by 15 ml/kg/hr by infusion – continue treatment for several days (methanol is oxidized slowly)
- ▶ Potassium chloride if hypokalemia occurs
- ▶ Folinic acid or Calcium leucovorin injection 50 mg IV every 6 Hourly – to enhance oxidation of formic acid
- ▶ 4-methylpyrazole(FOMEPIZOLE) – specific inhibitor of ALD – 15 mg/kg IV and 10 mg/kg 12 Hourly. till methanol level is <20 mg/dl
- ▶ Haemodialysis

Summary

- ▶ Alcohol is a neuronal depressant
- ▶ Long term exposure to alcohol brings about adaptive changes in the neuronal system
- ▶ Chronic alcoholism causes toxic effects on all the organs especially liver
- ▶ Withdrawal syndrome in alcoholics are treated by BZDs and Naltrexone
- ▶ Antbuse/disulfiram is the drug is use as aversion technique in chronic alcoholics
- ▶ Ethanol is used as antidote in Methanol Poisoning

Thank you

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