ALCOHOLS

- Hydroxy Derivatives of Aliphatic Hydrocarbons
- Misuse / Abuse

PHARMACOLOGICAL PROPERTIES

C.N.S.

NEURONAL DEPRESSANT PRIMARILY

Causes sedation & relief of anxiety

Lower Plasma conc. apparent excitement euphoria

- **30-100 mg/dl** Depression of inhibitory control mechanisms
- 1st mental processes to be affected: which depend on Training, memory, concentration.
- Insight dulled and lost, Slowing of Reflexes, Sleep.

> 300 mg/dl – Loss of consciousness- Anesthesia – Coma

> 500 mg/dl - Lethal.

- Tolerant need more conc. to elicit CNS effects

BLOOD ALCOHOL CONC. & CLINICAL EFFECTS

- 50-100mg/dl – sedation, subjective high, slower reaction time
- 100-200mg/dl – impaired motor function, slurred speech, ataxia
- 200-300mg/dl – emesis, stupor
- 300-400 mg/dl – coma
- >500 mg/dl – respiratory depression & death

CVS AND BLOOD VESSELS

- Small doses – Cutaneous and Gastric Vasodilatation > warm Flushed Skin.
- Moderate does - tachycardia and mild rise in BP
- Large doses – Direct myocardial and vasomotor centre depression > fall in BP.
- Long term Use - Dilated Cardiomyopathy and heart failure

  Regular , Small to moderate amount increases HDL

  Excessive use - MI

- ARRYTHMIAS –
- HEAVY DRINKING – BINGE DRINKING A/W ATRIAL & VENTRICULAR ARRYTHMIAS
- PTs. UNDERGOING WITHDRAWL SYNDROME CAN DEVELOP SEVERE ARRYTHMIAS
- CAD – CONTROVERSY
- BLOOD - MILD ANEMIAS RESULTING FROM ALCOHOL RELATED FOLIC ACID DEFICIENCY.
- IRON DEFICIENCY ANEMIA FROM GIT BLEEDING

RESPIRATORY SYSTEM

Large dose – Dangerous depression & Death

GIT

LIVER

- Accumulation of acetaldehyde – damages Hepatocyte.
- Alcoholic fatty Liver
- Alchoholic Hepatitis
- Cirrhosis
- Liver failure.
- depends on the Amount and Duration of alcohol consumption
- **Increased lipid peroxidation.**
- **Depletion of Glutathione.**
- **Depletion of vitamins and trace metals.**

KIDNEY-

- Diuretic effect
- Due to fluid taken with alcoholic beverages
- Inhibition of ADH secretion by alcohol

CHRONIC ALCOHOLISM

Liver - Fatty infiltration
Hepatitis
Cirrhosis

CVS - Hypertension- Heavy alcohol use
cardiac Arrhythmias
stroke- Hemorrhagic and Ischaemic

Endocrine effects -
Chronic Pancreatitis- Hyperglycemia
Acute intoxication - Hypoglycemia

- **<u>Vit and Minerals Deficiency</u>**
- decreased intake
- decreased absorption
- Impaired utilization of nutrients
- **Peripheral neuropathy** Def. of B- Complex Vit direct toxicity

- Korsakoff's psychosis
- Wernicke's encepalopathy

Osteoporosis - decreased bone osteoblastic activity

Sexual fx - Impaired

Blood - Anaemias -

Microcytic- Ch blood loss and Iron deficiency

Macrocytic anaemia and Normocytic anaemias

Thrombocytopenia

Leukopenia

Wernicke – Korsakoff syndrome

- Relatively uncommon but important entity characterised by-
- Paralysis of external eye muscles
- Ataxia
- Confused state – can Progress to coma and death
- a/w Thiamine deficiency.
- Shd be given thiamine therapy
- Ocular sign, ataxia and confusion improve promptly upon admin. of thiamine.
- But most pts are left with a chronic disabling memory disorder a **korsakoff's psychosis.**
- Over several wks of heavy alcohol consumption impaired visual acuity with painless blurring

MECHANISMS OF TS DAMAGE

- INCREASED OXIDATIVE STRESS
- COUPLED WITH DEPLETION OF GLUTATHIONE
- DAMAGE TO MITOCHONDRIA
- GROWTH FACTOR DYSREGULATION
- POTENTIATION OF CYTOKINE INDUCED INJURY

TERATOGENIC EFFECTS

- FOETAL ALCOHOL SYNDROME (FAS)
  LOW IQ, GROWTH RETARDATION ,
  MICROCEPHALY, FACIAL ABNORMALTIES
- Increased susceptibility to life - threatening and
  minor infectious diseases
- Impairment of immune system.
- at 75 ml / day FAS
- **STILL BIRTHS AND SPONTANEOUS ABORTIONS**

MOA

--- FACILITATION OF ACTION OF GABA AT GABA A RECEPTORS.

--- INHIBITION OF ABILITY OF GLUTAMATE TO ACTIVATE NMDA receptors (N methyl- D-aspartate)

MOA

- NMDA RECEPTOR IS IMPLICATED IN COGNITIVE FUNCTIONS , INCLUDING LEARNING & MEMORY
- PERIODS OF MEMORY LOSS THAT OCCUR WITH HIGH LEVELS OF ALCOHOL –MAY RESULT FROM INHIBITION OF NMDA RECEPTOR ACTIVATION

PHARMACOKINETICS

- PEAK BLOOD ALCOHOL CONC. IN 30 min.
- Women higher peak conc. than men.
- WOMEN HAVE LOWER TOTAL BODY WATER CONTENT
- ZEOR ORDER KINETICS
- 7-10 g alcohol metabolized/hour
- 90% oxidized in liver
- Rest through lungs and in urine.
- BREATH ALCOHOL TESTS (DRIVING UNDER INFLUENCE) 80-100 mg/dl – blood conc. For driving under influence in adults

TWO MAJOR PATHWAYS OF METABOLISM OF ALCOHOL

ALCOHOL DEHYDROGENASE PATHWAY

- ETHANOL -----↓---- ACETALDEHYDE
- **alcohol dehydrogenase**
- NAD------NADH ,

- **MICROSOMAL ETHANOL OXIDIZING SYSTEM**

ETHANOL ------MEOS------ACETALDEHYDE

(MICROSOMAL ETHANOL-OXIDIZING SYSTEM) NADPH-----NADP+

ACETALDEHYDE METABOLISM

ACTALDEHYDE ------↓- ACETATE ------CO 2 & H2O

aldehyde dehydrogenase

- **During conversion of ethanol to acetaldehyde, hydrogen ion is transferred from alcohol to the cofactor nicotinamide adenine dinucleotide (NAD+) to form NADPH.**

- **Alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH .**

- **The excess NADH production appears to contribute to a number of metabolic disorders that accompany chronic alcoholism.**

- Mixed function oxidase system uses NADPH , as a cofactor in the metabolism of ethanol , consists mainly of cytochrome P450 2E1, 1A2, 3A4
- At blood conc.> 100 / dl
- (During chronic alcohol consumption , MEOS is induced)
- Significant increase in ethanol metabolism & Clearance of other drugs eliminated by

  Cyto P450
- Increased generation of toxic byproducts (free radicals, H_2O_2

- **ACUTE ETHANOL INTOXICATION**

- At Conc. Of 150 mg/ dl _ Gross Intoxication
- Av. 500 mg/ dl – Fatal

  Saliva, Urine, Sweat, blood
- Levels in EXHALED AIR - Primary method

- Conc. Higher in Women ---
- Smaller than men.
- Less body water per unit of wt. into
- which alcohol can distribute
- Less gastric alcohol dehydrogenase activity.

HYPOTENSION, GASTRITIS, HYPOGLYCEMIA, COLLAPSE, RESPIRATORY DEPRESSION, COMA AND DEATH.

- **Rx –**
- INTUBATION
- MAITAIN PATENT AIRWAY
- +VE PRESSURE RESPIRATION , IF DEPRESSED
- GASTRIC LAVAGE (PREVENT PULMONARY ASPIRATION)
- MAINTAINENCE OF FLUID AND ELECTROLYTE BALANCE
- HEMODIALYSIS.

Withdrawl syndrome

upregulation of NMDA subtype of glutamate receptor & voltage sensitive Calcium channels leading to seizures.

Anxiety, sweating, & tremor, impairement of sleep, confusion, hallucinations, delirium tremens, convulsions, collapse.

Rx:- 1. BARBITURATES, PHENOTHIAZENES, BENZODIAZEPINES
2. OPIOID ANTAGONIST – NALTREXONE
3. ACAMPROSATE (NMDA ANATAGONIST)
4. PSYCHOLOGICAL AND MEDICAL SUPPORTIVE MEASURES.

Several months may be required for restoration of normal functions,esp sleep.

Alcoholism

Tolerance and Physical Dependence

- **Tolerance**
- Ethanol induced up-regulation of pathway in response to the continuous presence of ethanol.

- **Dependence -** From over activity of that same pathway after ethanol effect dissipates and before the system has time to return to a normal ethanol free state.

- **Withdrawal –** upregulation of NMDA subtype of glutamate receptor & voltage sensitive Calcium channels leading to seizures.

- **GABA** Main role in tolerance & withdrawal
- **Local conc. Of serotonin, opioids, dopamine affected – involved in brain reward circuit.**

Naltrexone

- Opioid Receptor antagonist
- Blocks activation by alcohol of dopaminergic pathways in the brain that are thought to be critical to reward.
- Decreases the urge to drink , Increases control.
- Works best when used along with some psychosocial therapy, such as Cognitive behavioral therapy.
- Administered after detoxification, at a dose of 50 mg/ day for several months.
- Most common S/E is --Nausea.
  In excessive doses, - Liver damage C/I in Liver failure or acute hepatitis
  Cautious use in Active liver ds patient.

Nalmefene

- Greator oral bioavailability
- Longer duration of action
- Lack of dose dependent problems with Liver toxicity.

ANTABUSE DISULFIRAM

- ALDEHYDE DEHYDROGENASE INHIBITOR
- ACCUMULATION OF ACETALDEHYDE
- ALCOHOLICS WHO ARE CO-OPERATIVE AND MOTIVATED.
- IMMEDIATE UNPLEASANTNESS
  FLUSHING, THROBBING HEADACHE, NAUSEA, VOMITING, SWEATING, HYPOTENSION, CONFUSION.
- Acetaldehyde conc. Increases 5-10 times

Acetaldehyde syndrome

- Slow elimination of drug.
- Effect for several days
- Also inhibits metabolism of other drugs
  PHENYTOIN , ORAL ANTICOAGULANTS
  ISONIAZID ,
  AVOID DISGUISED ALCOHOL

- COMPLIANCE LOW, EFFECTIVENESS WEAK, NOT COMMONLY USED

S/ES - Acneform eruptions, Urticaria, lassitude, Metallic taste, Tremor, Mild g.i disturbances , Peripheral neuropathies, headache, Restleness

Therapeutic use

- Chronic Alcoholism.
- 12 hours abstinence from alcohol needed
- Initially dose 500 mg. x 1-2 wks.
- Maintenance dose 125-500 mg daily
- Sensitization to alcohol may last as long as 14 days after test ingestion of disulfiram.

CLINICAL USES 0F ALCOHOL

- As antiseptic
- Counter- irritant for sprain , if pain.
- Rubbed onto skin to prevent bedsores.
- Alcohol sponges to decrease body temp.
- Intractable neuralgias
- Methanol poisoning.

Interactions of Alcohol with other Drugs:-

1. Stimulated by other agents which depress CNS

   Sedatives, hyponotics, anticonvulsants, antidepressants anti- anxiety , analgesic agents (opioids)

2. Decrease In clearance of phenytoin
   both drugs compete for same hepatic microsomal oxidase system.

3. But, in chronic drinker, enzyme induction, a period of abstinence - Increased clearance of phenytoin
   t ½ of tolbutamide decrease, Unpredictable fluctuations in plasma glucose with combination

- 4. Hepatotoxicity of Acetaminophen is increased-
- Increased formation of toxic intermediates
- Depletion of glutathione

5. Aldehyde dehydrogenase inhibitor -
   Metronidazole
   Cephalosporins

Oral hypoglycemics

METHANOL

- WOOD ALCOHOL
- USED IN INDUSTRIAL PRODUCTION OF SYNTHETIC COMPOUNDS ANDAS A CONSTITUENT OF MANY COMMERCIAL SOLVENTS
- WINDSHIELD WASHING PRODUCT

- POISONING
- DUE TO ACCIDENTAL INGESTION
- WHEN USED BY ALCOHOLICS AS AN ETHANOL SUBSTITUTE
- CAN BE ABSORBED THROUGH SKIN OR FROM RESPIRATORY OR GIT

Methanol

NAD ALCOHOL DEHYDROGENASE

↓

NADH

Formaldehyde

↓ Aldehyde Dehydrogenase

Formic Acid

↓ folate dependent

$Co_2 + H_2O$

Rate of oxidation – ½ of that of oxidation of ethanol.

Signs and Symptoms of methanol poisoning

VISUAL DISTURBANCE, LIKE BEING IN A SNOW STORM

Headache

Vertigo

Vomiting

Severe upper abdominal pain.

Back Pain

Dyspnoea

Motor Restlenness

Cold clammy extremities

Blurring of vision

Hyperemia of optic disc

Respiration- Slow, shallow, gasping- coma

Death – Resp. failure.

Lab test

- metabolic acidosis
- At Autopsy Pancreatic necrosis
- Soon after acidosis
- - Visual disturbance
  - Dilated pupils (Underactive)
  - Dim vision
- Changes in retina may be detected on examination
- Ocular lesions involve –
- ganglion cells of retina,Destructive inflammation, Atrophy
- Finally, Permanent Bilateral Blindness due to **formic acid , related to low tetrahydofolate**

MANAGEMENT

1. Correction of acidosis – Na bicarbonates.
2. Inhibition of methanol metabolism give ethanol loading dose 0.6 g/ Kg. intravenously.
3. Hemodialysis- blood methanol conc. > 500 mg/.
4. **Fomepizole**, 4-methylpyrazole - a specific inhibitor of alcohol dehydrogenase.
5. Folate and leucovorin, to enhance rate of metabolism of formate.
6. Neurological damage (Permanent motor dysfunction similar to parkinisonism) may follow – levodopa may relieve rigidity and hypokinesis.