chapter 28 Ethyl and Methyl Alcohols

ETHYL ALCOHOL (Ethanol)

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. When unqualified, 'alcohol' refers to *ethyl alcohol* or *ethanol*. Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history), alcoholism and for alcohol intoxication, rather than as a medicinal substance.

Alcohol is manufactured by fermentation of sugars:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow[(\textit{in yeast})]{\textit{Zymase}} 2CO_2 + \underset{\text{Ethanol}}{2C_2H_5OH}$$

Fermentation proceeds till alcohol content reaches ~ 15%. Then the reaction is inhibited by alcohol itself. Starchy cereals, e.g. barley, when soaked produce malt:

$$\text{STARCH} \xrightarrow{\textit{Convertase}} \text{MALTOSE}$$

which can then be fermented by yeast to produce alcohol. The major source of commercial alcohol is *mollases*, the leftover byproduct of sugar industry.

ALCOHOLIC BEVERAGES

There are a large variety of alcoholic beverages.

A. Malted liquors Obtained by fermentation of germinating cereals; these are undistilled—alcohol content is low (3–6%) e.g. Beers, Stout. Now strong beers (upto 10%) are also available.

B. Wines Produced by fermentation of natural sugars as present in grapes and other fruits. These are also undistilled.

Light wines Claret, Cider; alcohol content 9–12%, cannot exceed 15%.

Fortified wines Port, Sherry (alcohol 16–22%): distilled beverages are added from outside to the wine.

Effervescent wines Champagne (12–16% alcohol): these are bottled before fermentation is complete; the CO_2 produced after botteling remains dissolved under pressure.

Wines are called 'dry' when all sugar present has been fermented and 'sweet' when some is left.

C. Spirits These are produced by distillation of the fermented broth; e.g. Rum, Gin, Whiskey, Brandy, Vodka, etc. Though the alcohol content of these beverages can vary from 40–55%, in India (and almost internationally) for all licenced brands it is standardized to 42.8% v/v or 37% w/w.

The taste, flavour and value of various alcoholic beverages depends not only on alcohol content but on the presence of higher ethers, higher alcohols, aldehydes, esters, polymers, and volatile oils; many of which are formed during 'maturation' of the beverage.

Other forms of alcohol

1. *Absolute alcohol* 99% w/w ethanol (dehydrated alcohol).
2. *Rectified spirit* 90% w/w ethyl alcohol produced from fermented mollases, by distillation.
3. *Proof spirit* It is an old term. If whiskey is poured on gun powder and ignited and it explodes, then it was labelled to be of 'proof strength'. If water is mixed to it, the gun powder will not ignite. 100% proof spirit is 49.29% w/w or 57.1% v/v alcohol.
4. *Methylated spirit (industrial)* Also called 'denatured spirit' is produced by adding 5 parts of wood naphtha (methyl alcohol) to 95 parts of rectified spirit so as to render it unfit for drinking. It is tinted blue by methylene blue dye for distinction. It can be applied on the skin for antiseptic, cleaning and astringent purposes.

PHARMACOLOGICAL ACTIONS

1. Local actions Ethanol is a mild rubefacient and counterirritant when rubbed on the skin. By evaporation it produces cooling. Applied to delicate skin (scrotum) or mucous membranes it produces irritation and burning sensation. Concentrated alcohol (spirit) should not be applied in the mouth, nose, etc. Injected s.c. it causes intense pain, inflammation and necrosis followed by fibrosis. Injected around a nerve it produces permanent nerve damage.

Applied to the surface, alcohol is an astringent—precipitates surface proteins and hardens the skin. By precipitating bacterial proteins it acts as an antiseptic. The antiseptic action increases with concentration from 20 to 70%, remains constant from 70 to 90% and decreases above that. That 100% ethanol is more dehydrating but poorer antiseptic than 90% ethanol, shows that antibacterial action is not due to dehydration of bacterial protoplasm. Alcohol does not kill bacterial spores.

2. CNS Alcohol is a neuronal depressant. Since the highest areas are most easily deranged and these are primarily inhibitory—apparent excitation and euphoria are produced at lower plasma concentrations (30–60 mg/dl). Hesitation, caution, self-criticism and restraint are lost first. Mood and feelings are altered; anxiety may be allayed. At 50–100 mg/dl some individuals may experience what is labelled as 'high'. With increasing concentration (100–150 mg/dl) mental clouding, disorganization of thought, impairment of attention, memory and other faculties, alteration of gait and perception, and drowsiness supervene. At 150–200 mg/dl the person is sloppy, ataxic and drunk, 'black-outs' occur; 200–300 mg/dl result in stupor and above this unconsciousness prevails, medullary centres are paralysed and death may occur. Though, alcohol can produce anaesthesia, margin of safety is narrow.

Any measurable concentration of alcohol produces a measurable slowing of reflexes: driving is dangerous. Performance is impaired, fine discrimination and precise movements are obliterated; errors increase, except if fear of punishment and anxiety of failure has already impaired it. Under such situation performance may be improved by allaying of anxiety and fear.

At any given blood alcohol level, central effects are more marked when the concentration is rising than when it is falling. This is considered to be a manifestation of acute tolerance.

Alcohol can induce sleep but is not a dependable hypnotic. Some individuals report poor quality of sleep and repeated or early morning awakening. Sleep architecture may be disorganized and sleep apnoea aggravated. 'Hangover' (headache, dry mouth, laziness, disturbed mood, impaired performance) may occur the next morning. Alcohol raises pain threshold and also alters reaction to it, but is not a dependable analgesic—severe pain can precipitate confusion and convulsions. During the time alcohol is acting on the brain, it exerts anticonvulsant action, but this is followed by lowering of seizure threshold: seizures may be precipitated in epileptics. Chronic alcohol abuse damages brain neurones, causes shrinkage of brain.

The cortex and the reticular activating system are the most sensitive to alcohol; other areas get depressed as concentration rises.

Mechanism of action Alcohol was believed to produce CNS depression by a generalized membrane action altering the state of membrane lipids. However, lately specific effect on multiple receptor operated and voltage gated ion channels as well as other critical proteins has been demonstrated at concentrations attained during moderate drinking. Thus, several neurohumoral systems are concurrently affected producing a complex pattern of action quite different from

Alcohol : conscious → anaesthesia → death.

Ether : conscious → anaesthesia → death.

that produced by other depressants like barbiturates and benzodiazepines, which predominantly facilitate $GABA_A$ receptor mediated Cl^- channel opening. Alcohol has been shown to enhance GABA release at $GABA_A$ sites in the brain. It also inhibits NMDA type of excitatory amino acid receptors (operating through cation channels) which has been implicated in memory impairment caused by alcohol. Action of 5-HT on $5\text{-}HT_3$ inhibitory autoreceptor (having an intrinsic ion channel) is augmented. Some studies suggest that cerebral nicotinic cholinergic receptor (operating through Na^+ channel) may also be one of the targets of alcohol action. Ethanol can indirectly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{2+} channels. It also activates specific type of K^+ channels in certain brain areas. Release and turnover of DA in brain is enhanced through β endorphin release in nucleus accumbens and an opioid receptor dependent mechanism. This is probably important in the pleasurable reinforcing effects of alcohol and in the 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.

3. CVS The effects of alcohol are dependent on the dose.

Small doses: produce only cutaneous (especially 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 a 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.

Epidemiological studies have confirmed that chronic alcoholism contributes to hypertension and can lead to cardiomyopathy. Atrial fibrillation and other cardiac arrhythmias may occur due to conduction defects and Q-T prolongation.

4. Blood Regular intake of small to moderate amounts of alcohol (1–2 drinks) has been found to raise HDL-cholesterol levels and decrease LDL oxidation. This may be responsible for the 15–35% lower incidence of coronary artery disease in such individuals. Risk reduction is greatest in high risk subjects and protection is lost if ≥ 3 drinks are consumed daily. However, it is considered inappropriate nondrinkers to start drinking on this since other adverse consequences may m nullify this benefit. Mild anaemia is c in chronic alcoholics. Megaloblastic a occurring in chronic alcoholism is d interference with folate metabolism.

5. Body temperature Alcohol is rep to combat cold. It does produce a sense warmth due to cutaneous and gastric vaso latation, but heat loss is actually increased cold surroundings. Drinking before going ou in the cold is inadvisable. High doses depress temperature regulating centre.

6. Respiration Brandy or whiskey are reputed as respiratory stimulants in collapse. They irritate buccal and pharyngeal mucosa which may transiently stimulate respiration reflexly. However, it is better not to depend on this, because the direct action of alcohol on respiratory centre is only a depressant one.

7. GIT Alcoholic beverages have variable effect on gastric secretion depending on the beverage itself and whether the individual likes it. However, dilute alcohol (optimum 10%) put in the stomach by Ryle's tube is a strong stimulant of gastric secretion (especially of acid). It acts directly as well as reflexly. Higher concentrations (above 20%) inhibit gastric secretion, cause vomiting, mucosal congestion and gastritis. Alcoholism is an important cause of chronic gastritis. Lower esophageal sphincter (LES) tone is reduced by alcohol. Drinking may accentuate gastric reflux. Bowel movements may be altered in either direction. Acute pancreatitis is a complication of heavy drinking.

8. Liver Neither brief alcohol intoxication nor chronic intake of small-to-moderate amounts cause significant liver damage, provided adequate nutrition is maintained. However, it does mobilize peripheral fat and increases fat synthesis in liver in a dose-dependent manner producing 'fatty liver'. This is reversible, but may progress to cirrhosis if prolonged or excessive. Proteins may also accumulate in liver because their secretion is decreased. Chronic alcoholism

exposes liver to oxidative stress and causes cellular necrosis followed by fibrosis. Acetaldehyde produced during metabolism of alcohol appears to damage the hepatocytes and induce inflammation, especially on chronic ingestion of large amounts. Increased lipid peroxidation and glutathione depletion occurs. These combined with vitamin and other nutritional deficiencies may be responsible for the so called *alcoholic cirrhosis*.

Regular alcohol intake induces microsomal enzymes.

9. Skeletal muscle Alcohol produces little direct effect. Fatigue is allayed by small doses, but muscle work is increased or decreased depending on the predominating central effect. Weakness and myopathy occurs in chronic alcoholism.

10. Kidney Diuresis is often noticed after alcohol intake. This is due to water ingested along with drinks as well as alcohol induced inhibition of ADH secretion. Alcohol does not impair renal function.

11. Sex Alcohol is reputed as an aphrodisiac. Though, loss of restraint and inhibition may provoke sexual behaviour in some individuals or on some occasions, there is no uniform effect of alcohol on sexual desire. Moreover, performance of the sexual act is often impaired. Chronic alcoholism can produce impotence, testicular atrophy, gynaecomastia and infertility in both men and women.

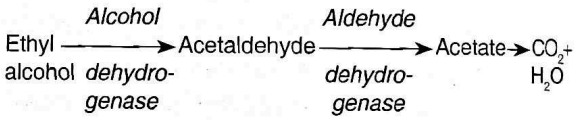
12. Endocrine effects Moderate amounts of alcohol increase Adr release which can cause hyperglycaemia and other sympathetic effects. However, acute intoxication is often associated with hypoglycaemia and depletion of hepatic glycogen, because gluconeogenesis is inhibited. Glucagon, therefore fails to reverse alcohol induced hypoglycaemia, and glucose must be given to counteract it.

13. Uterine contractions are suppressed at moderate blood levels.

PHARMACOKINETICS

Rate of alcohol absorption from the stomach is dependent on its concentration, presence of food, and other factors, but is generally quite slow. Absorption from intestines is very fast; peak levels after ingestion in the fasting state are attained after ~30 min. Thus, gastric emptying determines the rate of absorption. Limited first pass metabolism occurs in stomach and liver. Absorption of alcohol from skin of adults is minimal but may be significant in infants given alcohol sponges.

Alcohol gets distributed widely in the body (vol of distribution 0.7 L/kg, i.e. equal to volume of total body water), crosses blood-brain barrier efficiently: concentration in the brain is very near blood concentration. It also crosses placenta freely. Alcohol is oxidized in liver to the extent of 98%. Even with high doses, not more than 10% escapes metabolism. The primary pathway sequentially utilizes alcohol dehydrogenase and aldehyde dehydrogenase.



Alcohol dehydrogenase exhibits considerable genetic variability which is reflected in the rate at which individuals metabolize alcohol, and probably governs their susceptibility to alcohol.

In addition to alcohol dehydrogenase, small amounts of alcohol are oxidized by hepatic microsomal enzymes (mainly CYP2E1) as well. Metabolism of alcohol follows *zero order* kinetics, i.e. a constant amount (8–12 ml of absolute alcohol/ hour) is degraded in unit time, irrespective of blood concentration. Thus, the rate of consuming drinks governs whether a person will get drunk.

Excretion of alcohol occurs through kidney and lungs, but neither is quantitatively significant. Concentration in exhaled air is about 0.05% of blood concentration. This is utilized for medicolegal determination of drunken state. The subject blows in a portable hand-held

breath-analyser which measures the alcohol content of exhaled air and displays the result in terms of corresponding blood alcohol concentration (mg/dl).

INTERACTIONS

1. Alcohol synergises with anxiolytics, antidepressants, antihistaminics, hypnotics, opioids, so that marked CNS depression with motor impairment can occur. Chances of accidents increase.
2. Some individuals taking a sulfonylurea, cefoperazone, or metronidazole have experienced bizarre, somewhat disulfiram-like reactions when they consume alcohol. This reaction occurs only in few individuals and its basis is unclear. It passes off with time as alcohol is metabolized. Only reassurance and supportive treatment is needed.
3. Acute alcohol ingestion inhibits, while chronic intake induces CYP enzymes (especially CYP2E1). Formation of toxic metabolite of paracetamol (NABQI) is increased in chronic alcoholics (*see* p. 224). Safe dose limit of paracetamol is lower in them. Metabolism of tolbutamide, phenytoin and some other drugs is similarly affected by acute and chronic alcohol intake.
4. Hypoglycaemic action of insulin and sulfonylureas is enhanced by alcohol ingestion.
5. Aspirin and other NSAIDs cause more gastric bleeding when taken with alcohol.

Food value

Alcohol requires no digestion and is metabolized rapidly. It is an energy yielding substrate: 7 Cal/g, but these cannot be stored. However, it spares carbohydrates and fats as energy source, so that regular intake can contribute to obesity. Alcohol does not supply body building and other essential constituents of food. Those who consume substantial part of their caloric intake as alcohol, often suffer from nutritional deficiencies. Thus, alcohol is an imperfect and expensive food.

CONTRAINDICATIONS

Alcohol is seldom prescribed medically. However, it is rampently consumed. Intake of alcohol should be avoided by—

1. Patients with peptic ulcer, hyperacidity and gastroesophageal reflux disease (alcohol increases gastric secretion and relaxes LES).
2. Epileptics: seizures may be precipitated.
3. Severe liver disease patients.
4. Unstable personalities: they are likely to abuse it and become excessive drinkers.
5. Pregnant women: Even moderate drinking during pregnancy can produce *foetal alcohol syndrome* resulting in intrauterine and postnatal growth retardation, low IQ offspring, microcephaly, cranio-facial (flat face) and other abnormalities, and immunological impairment causing increased susceptibility to infections. Heavy drinking during pregnancy, in addition, increases the incidence of miscarriage, stillbirths and low birth-weight babies.

Guidelines for safe drinking Alcoholic beverages are widely consumed, and in many cultures they are served as a part of social courtesy. Moderate drinking is generally considered socially acceptable. Physicians are often asked to advise on safe ways of drinking. Various official agencies, physician organizations and alcoholism experts have putforth guidelines in this regard, but they are not uniform. The following may be concluded:

- On an average 1–2 drinks per day is usually safe.
- Not more than 3 drinks on any one occasion.
- Consumption of >3 drinks per day is associated with documented adverse health effects.
- Do not drive or engage in hazardous activities after drinking.
- Do not drink if an interacting drug has been taken.
- Subjects with any contraindication should not drink.
- Safe limits are somewhat lower for women than for men, because metabolism of alcohol

is slower and its bioavailability higher (due to less first pass metabolism in stomach) in women than in men.

[Note: 1 drink = 50 ml of spirits = 150 ml of wines = 400 ml of beer; all have roughly 16 g alcohol, which taken in empty stomach produces a peak alcohol blood level of ~ 30 mg/dl in an adult male of average built.]

TOXICITY

A. *Side effects of moderate drinking* Nausea, vomiting, flushing, hangover, traffic accidents.

B. *Acute alcoholic intoxication* Unawareness, unresponsiveness, stupor, hypotension, gastritis, hypoglycaemia, respiratory depression, collapse, coma and death.

Treatment: Gastric lavage is helpful only when the patient is brought soon after ingesting alcohol, which is rare. Since most patients are disoriented or comatose, the first priority is to maintain patent airway and prevent aspiration of vomitus. Tracheal intubation and positive pressure respiration may be needed if it is markedly depressed. Analeptics should not be given. They may precipitate convulsions. Most patients will recover with supportive treatment, maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion till alcohol is metabolized. Thiamine (100 mg in 500 ml glucose solution infused i.v.) should be added. Recovery can be hastened by haemodialysis. Insulin + fructose drip has been found to accelerate alcohol metabolism. However, its clinical impact is not remarkable.

C. *Chronic alcoholism* On chronic intake, tolerance develops to subjective and behavioural effects of alcohol, but is generally of a low degree. It is both pharmacokinetic (reduced rate of absorption due to gastritis and faster metabolism due to enzyme induction) and cellular tolerance. Mild addiction occurs in some subjects even with moderate drinking. It depends a lot on the individual's likings and attitudes. Addiction is manifested in alcohol-seeking behaviour, and the priority that the subject accords to obtaining and consuming alcohol over other needs, or the extent to which he will go for maintaining alcohol intake.

Recent studies have confirmed that a genetic basis contributes to progression from social drinking to alcoholism in about 50% individuals. Alcoholism is often a familial trait. Some differences in sensitivity of various neuronal systems to alcohol among 'predisposed' and 'not predisposed' individuals have been demonstrated.

There is no single explanation for why people drink. Diverse feelings and behaviours are provoked by alcohol in different individuals and in the same individual on different occasions. Alcohol can make people happy as well as sad, curtious as well as mean, talkative as well as silent, friendly as well as hostile. All this cannot be explained on the basis of pharmacological actions of alcohol alone. Attitudes, beliefs, peer groups, social setting and learned experiences all have a bearing. Alcohol is said to produce good mood, sense of wellbeing, self confidence, sociability, etc. But these infact are learned behaviours. In some societies, alcoholic beverages have become an acceptable form of extending courtesy and of entertainment. Drinking is often related to 'celebration' and 'high living'. There is 'wine snobbery' in high social groups.

To some individuals, excess drinking provides the excitement of risk taking. People often boast of their capacity to drink. To the young, drinking may be a symbol of rebellion against the oppressive older generation and rejection of the values of the establishment. 'Binge drinking' is a specific behavioural pattern of bouts of excessive drinking. Alcohol is often an excuse for bad behaviour. Society's view that intoxicated person is unaware of his actions (therefore not responsible) makes intoxication an attractive state, because there is increased freedom of what one can say or do after drinking. Thus, there are a variety of motivations for drinking.

Alcohol dependence occurs only on heavy and round-the-clock drinking (if alcohol is present in the body continuously). Heavy drinking is often associated with nutritional deficiencies, because food is neglected and malabsorption may occur. In addition to impaired mental and physical performance, neurological afflictions are common—polyneuritis, pellagra, tremors, seizures, loss of brain mass, Wernicke's encephalopathy, Korsakoff's psychosis and megaloblastic anaemia. Thiamine deficiency is very common in chronic alcoholism; and high dose thiamine injection partly reverses many neurological symptoms. Alcoholic cirrhosis of liver, hypertension, cardiomyopathy, CHF, arrhythmias, stroke, acute pancreatitis, impotence, gynaecomastia, infertility

and skeletal myopathy are the other complications. Incidence of oropharyngeal, esophageal and hepatic malignancy and respiratory infections is high; immune function is depressed.

Withdrawal syndrome When an alcohol dependent subject stops drinking, withdrawal syndrome appears within a day. Its severity depends on the duration and quantity of alcohol consumed by the subject. It consists of anxiety, sweating, tachycardia, tremor, impairment of sleep, confusion, hallucinations, delirium tremens, convulsions and collapse.

Treatment Psychological and medical supportive measures are needed during withdrawal. Many CNS depressants like barbiturates, phenothiazines, chloral hydrate have been used as substitution therapy in the past (to suppress withdrawal syndrome) but benzodiazepines (chordiazepoxide, diazepam) are the preferred drugs now. These drugs have a long duration of action and can be gradually withdrawn later.

Naltrexone: Several studies have demonstrated involvement of opioid system in the pleasurable reinforcing effects of alcohol through dopamine mediated reward function. Post-addict subjects treated with the long-acting opioid antagonist naltrexone (*see* Ch. 34) do not experience the same pleasurable effects on taking alcohol; reinforcement is weakened. Trials have shown that it helps prevent relapse of alcoholism. Naltrexone reduced alcohol craving, number of drinking days and chances of resumed heavy drinking. It is approved for use as adjuvant in comprehensive treatment programmes for alcohol dependent subjects and is being used in India at most deaddiction centres, after the individual has undergone withdrawal and is motivated.

Acamprosate It is a weak NMDA-receptor antagonist with modest $GABA_A$ receptor agonistic activity that is being used in USA, UK and Europe for maintenance therapy of alcohol abstinence. In conjunction with social and motivational therapy, it has been found to reduce relapse of the drinking behaviour. The efficacy of acamprosate in this regard is rated comparable to naltrexone. It should be started soon after withdrawing alcohol and then given continuously at a dose of 666 mg 2–3 times a day. Loose motion is a common side effect. Others are nausea, abdominal pain and itching.

The 5-HT_3 antagonist *ondansetron* and the antiepileptic *topiramate* have also shown some promise in treating alcoholism.

CLINICAL USES

Medicinal uses of ethanol are primarily restricted to external application and as a vehicle for liquid preparations used internally.

1. As antiseptic (*see* Ch. 67).
2. Rubefacient and counterirritant for sprains, joint pains, etc. Spirit is generally used as vehicle for other ingredients.
3. Rubbed into the skin to prevent bedsores; works by hardening the skin due to its astringent property. However, alcohol should not be applied on already formed sores. The astringent action of alcohol is also utilized in antiperspirant and aftershave lotions.
4. Alcoholic sponges have been used to reduce body temperature in fever. However, cold water/ice may be better.
5. Intractable neuralgias (trigeminal and others), severe cancer pain: Injection of alcohol round the nerve causes permanent loss of transmission.
6. To ward off cold. Alcohol in the form of whiskey or brandy may benefit by causing vasodilatation of blanched mucosae; but further exposure after taking alcohol may be deleterious because alcohol increases heat loss due to cutaneous vasodilatation.
7. As appetite stimulant and carminative: 30–50 ml of 7–10% alcohol may be taken as beverages or as tinctures (of ginger/cardemom, etc.) before meal.
8. To treat methanol poisoning (*see* below).

Aldehyde dehydrogenase inhibitor

Disulfiram It inhibits the enzyme aldehyde dehydrogenase (Fig. 28.1) probably after conversion into active metabolites. When alcohol is ingested after taking disulfiram, the concentration of acetaldehyde in tissues and blood rises and a number of highly distressing symptoms (aldehyde syndrome) are produced promptly. These are—flushing, burning sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances,

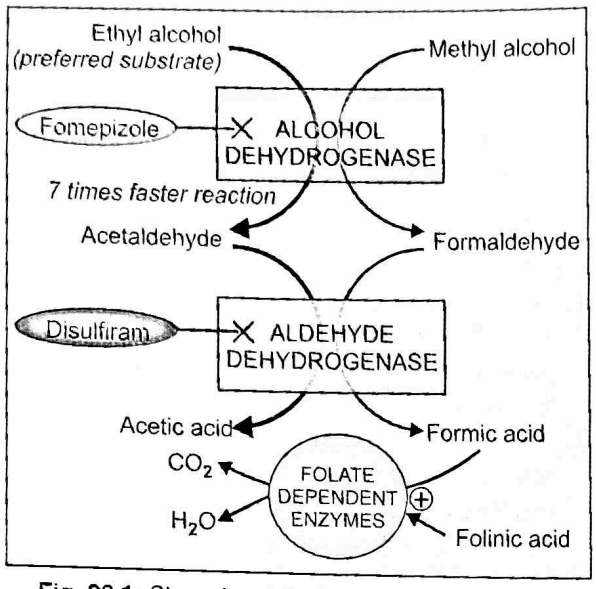


Fig. 28.1: Shared metabolic pathway of ethyl and methyl alcohols

mental confusion, postural fainting and circulatory collapse. Duration of the syndrome (1–4 hours) depends on the amount of alcohol consumed. Because of risk of severe reaction, disulfiram is to be used with great caution, only in well-motivated subjects.

Disulfiram aversion therapy is indicated in abstinent subjects who sincerely desire to leave the habit. After making sure that the subject has not taken alcohol in the past 12 hours, disufiram is given at a dose of 500 mg/day for one week followed by 250 mg daily. Sensitization to alcohol develops after 2–3 hours of first dose, reaches its peak at ~12 hours and lasts for 7–14 days after stopping it, because inhibition of aldehyde dehydrogenase with disulfiram is irreversible: synthesis of fresh enzyme is required for return of activity. The subject's resolve not to drink is reinforced by the distressing symptoms that appear if he drinks a little bit. The subject should be cautioned to avoid alcohol altogether. Disulfiram should not be given to patients who are physically dependent on alcohol.

Side effects of disulfiram (as such) are infrequent, include rashes, metallic taste, nervousness, malaise and abdominal upset. It inhibits a number of other enzymes as well including alcohol dehydrogenase, dopamine β hydroxylase and several cytochrome P450 isoenzymes. Thus, it prolongs t½ of many drugs.

ESPERAL, ANTADICT, DEADICT 250 mg tab. (internationally marketed as ANTABUSE)

METHYL ALCOHOL (Methanol, Wood alcohol)

Methyl alcohol is a commonly used industrial solvent and constituent of cleaning products. It is also added to industrial rectified spirit to render it unfit for drinking. It is only of toxicological importance. Mixing of methylated spirit with alcoholic beverages by bootlegers or its inadvertent ingestion results in methanol poisoning.

Methanol is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydrogenases respectively (Fig. 28.1), but the rate is 1/7th that of ethanol. Like ethanol, metabolism of methanol also follows *zero order* kinetics and t½ of 20–60 hours has been measured.

Methanol also is a CNS depressant, but less inebriating than ethanol. Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent. A blood level of >50 mg/dl methanol is associated with severe poisoning. Even 15 ml of methanol has caused blindness and 30 ml has caused death; fatal dose is regarded to be 75–100 ml.

Manifestations of methanol poisoning appear after a delay of few hours when its toxic metabolites accumulate. These are vomiting, headache, epigastric pain, uneasiness, drunkenness, disorientation, tachypnoea, dyspnoea, bradycardia and hypotension. Delirium and seizures may occur and the patient may suddenly pass into coma. *Acidosis* is prominent and entirely due to production of formic acid. The specific toxicity of formic acid is *retinal damage*. Blurring of vision, congestion of optic disc followed by blindness always precedes death which is due to respiratory failure.

Treatment

1. Keep the patient in a quiet, dark room; protect the eyes from light.

2. Gastric lavage with sod. bicarbonate if the patient is brought within 2 hours of ingesting methanol. Supportive measures to maintain ventilation and BP should be instituted.
3. Combat acidosis by i.v. *Sod. bicarbonate* infusion. This is the most important measure, which prevents retinal damage and other symptoms; large quantities may be needed.
4. Pot. chloride infusion is needed only when hypokalemia occurs due to alkali therapy.
5. *Ethanol* is preferentially metabolized by alcohol dehydrogenase over methanol. At a concentration of 100 mg/dl in blood it saturates alcohol dehydrogenase and retards methanol metabolism. This helps by reducing the rate of generation of formaldehyde and formic acid. Ethanol (10% in water) is administered through a nasogastric tube; loading dose of 0.7 ml/kg is followed by 0.15 ml/kg/hour. Because pharmacokinetics of alcohol changes over time and no i.v. formulation is available, maintenance of uniform blood alcohol concentration is difficult. Alcohol blood level needs to be repeatedly measured. Moreover, the enzyme saturating concentration of ethanol itself produces intoxication and can cause hypoglycaemia. Use of ethanol for this purpose is tricky. Treatment has to be continued for several days because the sojourn of methanol in body is long.
6. Haemodialysis: clears methanol as well as its toxic metabolite–formate and hastens recovery.
7. *Fomepizole* (4-methylpyrazole) is a specific inhibitor of alcohol dehydrogenase and the drug of choice for methanol poisoning, which acts by retarding its metabolism. A loading dose of 15 mg/kg infused i.v. over 30 min is followed by 10 mg/kg every 12 hours till serum methanol falls below 20 mg/dl. This has been found effective and safe, and has several advantages over ethanol, *viz.* longer t½, lack of inebriating action, and i.v. dosage form for regulated administration. Marketed elsewhere as ANTIZOL, it is not available commercially in India.

   Adverse effects of fomepizole are burning pain in infused limb, headache, nausea, taste disturbance and hypotension.
8. Folate therapy: Calcium leucovorin 50 mg injected 6 hourly has been shown to reduce blood formate levels by enhancing its oxidation. This is a promising adjuvant approach.

Ethylene glycol poisoning Ethylene glycol poisoning has occurred sporadically, especially among children. It is an industrial solvent, coolant and antifreeze. Ethylene glycol is oxidized in the body by alcohol dehydrogenase to glycoaldehyde and then to glycolic acid—glyoxylic acid—oxalic acid in steps. Ethylene glycol itself can cause intoxication similar to ethanol, but generation of metabolites results in acidosis, cardiopulmonary complications and renal tubular necrosis.

Fomepizole used in the same manner as for methanol poisoning is the drug of choice. It is approved by US-FDA for this indication and has 'orphan drug status'. Ethanol is employed as an alternative.

PROBLEM DIRECTED STUDY

28.1 A school boy aged 16 years developed tonic-clonic epilepsy and was maintained on carbamazepine 200 mg 3 times a day. He was seizure free for the last one year, but reported back one afternoon with the complaint of recurrence of two seizure episodes since morning. On questioning, he revealed that last evening he attended a party with his friends and consumed 4 drinks of whiskey, and was awake till late night. This was the first time that he had taken an alcoholic drink.

(a) Could the recurrence of seizures be related to the intake of alcohol previous night? If so, what could be the mechanism?

(b) Does his antiepileptic therapy need any change or adjustment of doses due to this recurrence of seizures. What further advise will you give to this patient?

(see Appendix-1 for solution)