CHAPTER 18

Alcohols and Disulfiram

ETHYL ALCOHOL (ETHANOL)

Ethyl alcohol is a monohydroxy alcohol manufactured by fermentation of sugars. It is a colourless, volatile, inflammable liquid. The ethanol content of various alcoholic beverages ranges from 4 to 55%. For commercial use, alcohol is largely produced from mollases which is a byproduct when sugar is manufactured from sugarcane.

Actions

1. ***Local:*** On topical application, ethanol evaporates quickly and has a cooling effect. It is an astringent—precipitates surface proteins and hardens the skin. 40–50% alcohol is a rubefacient and counterirritant. Alcohol is also an antiseptic. **At 70%, it has maximum antiseptic properties,** which decreases above that. It is not effective against spores.
2. ***CNS:*** Alcohol is a CNS depressant. Small doses cause euphoria, relief of anxiety and loss of social inhibitions. Moderate doses, blunt the reflexes and impair muscular coordination and visual acuity making driving dangerous. With higher doses, mental clouding, impaired judgement, fine and precise movement, drowsiness and loss of self-control result. High doses cause stupor and coma. Death is due to respiratory depression.

   Alcohol may precipitate convulsions in epileptics. Tolerance develops on long-term use.
3. ***CVS:*** The actions are dose dependent. Small doses cause cutaneous vasodilation resulting in flushing and feeling of warmth. Large doses cause hypotension due to depression of myocardium and vasomotor centre. Arrhythmias may also be seen in heavy drinking or 'binge drinking'. Chronic heavy drinking is associated with hypertension.

   Chronic moderate drinking, however, has shown to prevent coronary heart disease and stroke. It could be because of raised HDL, raised tissue plasminogen activator and because it could also inhibit inflammatory processes in atherosclerosis.
4. ***GIT and liver:*** Alcohol is an irritant—increases gastric secretion and produces vasodilation and warmth. It is an appetizer. Chronic alcoholism results in chronic gastritis.

   Chronic consumption of moderate amounts of alcohol results in accumulation of fat in the liver, liver enlargement, followed by fatty degeneration and cirrhosis.

   Alcohol induces hepatic microsomal enzymes.

Heavy drinking is associated with both acute pancreatitis and chronic pancreatitis.

5. *Other effects*
   - Though alcohol is called an aphrodisiac, this effect could be due to loss of inhibition.
   - Low doses taken over a long time increases HDL and lowers LDL cholesterol.
   - Alcohol is a diuretic (↓ADH secretion).
   - It interferes with folate metabolism and may cause megaloblastic anaemia.
   - Chronic alcoholics also develop nutritional deficiencies including vitamin deficiencies.
   - Chronic alcoholism is often associated with osteoporosis though the exact cause is not known.
   - Though alcohol causes a feeling of warmth, heat loss is increased due to vasodilation and should not be used for 'warming up' in cold surroundings. Food value is 7 calories/gram.

Mechanism of Action

Ethanol acts by:

1. Inhibiting nicotinic cholinergic receptors in the central neurons
2. Inhibiting excitatory NMDA and kainate receptor functions.
3. Promoting the function of 5-HT_3 receptors.
4. Also by influencing many ion channels including K^+ channels.

Pharmacokinetics

Alcohol is rapidly absorbed from the stomach and is metabolised in the liver by dehydrogenases (Fig. 18.1).

Metabolism follows zero order kinetics—a constant amount is metabolised per unit time, i.e. about 10 ml absolute alcohol is metabolised per hour. Hence, when higher doses are taken blood alcohol rises significantly resulting in toxicity. It is excreted through kidneys and lungs.

Drug Interactions

1. Alcohol potentiates other CNS depressants including hypnotics, opioids and antipsychotics.
2. Sulfonylureas, metronidazole and griseofulvin have disulfiram like effects on alcohol consumption—should be avoided.
3. Alcohol is an enzyme inducer and can hasten the metabolism of other drugs.
4. Alcohol increases gastric acidity which gets added up, if patients also receive NSAIDs and other gastric irritants.

Uses

1. *Antiseptic:* 70% alcohol is applied topically.
2. *Bedsores:* When rubbed on to the skin, alcohol hardens the skin and prevents bedsores—it is an astringent.
3. *Fever:* Alcoholic sponges are used for reduction of body temperature in fevers.
4. *Appetite stimulant:* About 50 ml of 6–10% alcohol given before meals is an appetite stimulant.
5. *Neuralgias:* In severe neuralgias like trigeminal neuralgia, injection of alcohol around the nerve causes permanent loss of transmission and relieves pain.
6. *In methanol poisoning* (*see* page 187).

Acute Alcoholic Intoxication

Acute alcoholic intoxication causes severe gastritis, hypotension, hypoglycaemia, respiratory depression, coma and death. Fatal blood alcohol concentration is >400 mg/dl but

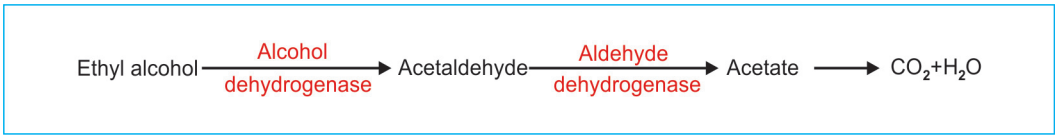


Fig. 18.1: Metabolism of ethanol

varies due to tolerance in chronic alcoholics. Treatment measures include gastric lavage, airway maintenance, positive pressure ventilation and maintenance of fluid and electrolyte balance. Haemodialysis is needed in severe intoxication. Hypoglycemia needs glucose; thiamine should be administered to prevent Wernicke's encephalopathy. Blood potassium and phosphate should be checked and corrected, if required.

Chronic Alcoholism

Chronic alcoholism causes dependence. Wernicke's encephalopathy, Korsakoff's psychosis, tremors, cirrhosis of liver, hypertension and cardiomyopathy can occur. In addition, nutritional deficiencies such as polyneuritis, anaemia and pellagra can occur. Chronic alcoholism is also associated with increased risk of cancer of the oropharynx, larynx, oesophagus and liver. In pregnant women, alcohol is teratogenic. Even moderate drinking during pregnancy can produce **fetal alcohol syndrome** with manifestations like low IQ, microcephaly, growth retardation and facial anomalies. It can also cause stillbirths and abortions.

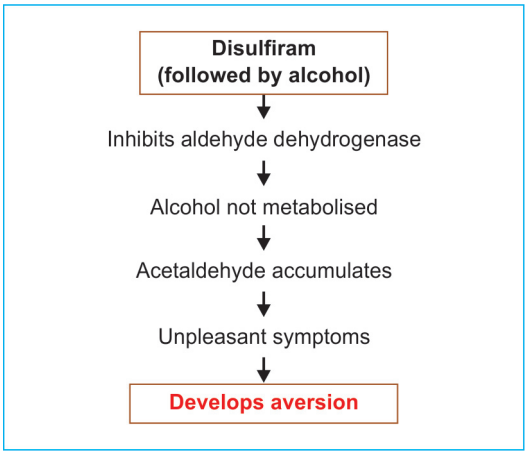
Drugs used in Alcohol Dependence

Alcohol dependence is a common social evil which is difficult to treat.

Abrupt withdrawal: Sudden cessation of alcohol in chronic alcoholics results in withdrawal symptoms including anxiety, tremors, insomnia, increased motor activity and reduced threshold for seizures which are prominent for 1–2 days but may persist in milder form for many months. Diazepam helps overcome most withdrawal symptoms. Other measures include correcting electrolyte imbalance, thiamine replacement, watching for seizures and treatment of seizures, if any, and reassurance.

Several drugs are tried in **chronic alcoholism**

1. **Disulfiram** is used to make alcohol consumption an unpleasant experience so that the person gives up drinking. Disulfiram inhibits the enzyme aldehyde dehydrogenase. If alcohol is consumed after taking disulfiram, acetaldehyde accumulates and within a few minutes it can produce flushing, throbbing headache, nausea, vomiting, sweating, hypotension and confusion—called **the antabuse reaction,** due to accumulation of acetaldehyde. The effect lasts for 7–14 days after stopping disulfiram. Therefore, the person develops aversion to alcohol and often gives up the habit.



However, willingness on the part of the person to give up the habit goes a long way in the success of this aversion therapy. The reactions can sometimes be very severe and, therefore, treatment should be given in a hospital.

Other drugs that cause antabuse reaction (Key Box 18.1).

Contraindications: Patients with liver disease, patients physically dependent on alcohol.

Key Box 18.1: Some drugs that can precipitate disulfiram-like reaction

Metronidazole	Some cephalosporins
Sulfonylureas	Phenylbutazone
Griseofulvin	Nitrofurantoin

2. **Benzodiazepines:** Long-acting BZDs like diazepam to reduce the symptoms of alcohol withdrawal—benzodiazepines relieve symptoms like anxiety and insomnia. They should be continued and gradually tapered over several months.

3. **Clonidine,** an α_2-receptor agonist, reduces the release of sympathetic neurotransmitters while propranolol blocks the effects of sympathetic overactivity like tremors and tachycardia.

4. **Naltrexone** is an orally effective opioid antagonist which has been thought to be useful in alcohol withdrawal. It is given in the dose of 50 mg once daily. A long-acting IM preparation to be given once a month is also available. Several studies have shown naltrexone to reduce alcohol craving and 'relapse' of heavy drinking. Naltrexone can cause nausea. Naltrexone and disulfiram should not be given concurrently as both can cause hepatotoxicity. Moreover, chronic alcoholics are likely to have an already damaged liver. **Nalmefene** can also be used in place of naltrexone.

5. **Acamprosate,** an NMDA receptor antagonist, has been found to be useful in preventing relapse of heavy drinking and in achieving alcohol abstinance.

6. **Ondansetron,** a 5-HT_3 antagonist antiemetic, has been shown to reduce alcohol consumption and is being evaluated for use in alcohol withdrawal.

7. **Other drugs:** Baclofen, a $GABA_B$ receptor antagonist, and topiramate, an antiepileptic drug, are tried. **Rimonabant,** a CB_1 cannabinoid receptor antagonist, has also been found to be useful in alcohol withdrawal.

8. **Psychosocial therapy** and counselling by a psychologist also help.

METHYL ALCOHOL (METHANOL, WOOD ALCOHOL)

Methanol is used to denature ethyl alcohol. It has no therapeutic value. Ingestion results in methanol poisoning. Methanol can also be absorbed through the skin. Methanol is converted to formaldehyde—catalysed by alcohol dehydrogenase; formaldehyde is converted to formic acid by the action of aldehyde dehydrogenase (Fig. 18.2). Toxic effects are due to formic acid.

Manifestations of toxicity may take about 30 hr to appear as they are due to the metabolites and include vomiting, headache, visual distrubances, vertigo, severe abdominal pain, hypotension, delirium, acidosis and coma. Formic acid has affinity for optic nerve and causes retinal damage resulting in blindness. There are reports of even 15 ml of methanol causing blindness. Death is due to respiratory failure.

Treatment

1. *Correction of acidosis:* As acidosis hastens retinal damage, immediate correction of acidosis with IV sodium bicarbonate infusion helps in preventing blindness.
2. *Protect eyes:* Patient should be kept in a dark room to protect the eyes.
3. *Gastric lavage:* Should be given.
4. *BP and ventilation:* Must be maintained.
5. *Ethyl alcohol:* Should be given immediately. It competes with methanol for alcohol dehydrogenase because of its higher affinity for alcohol dehydrogenase.

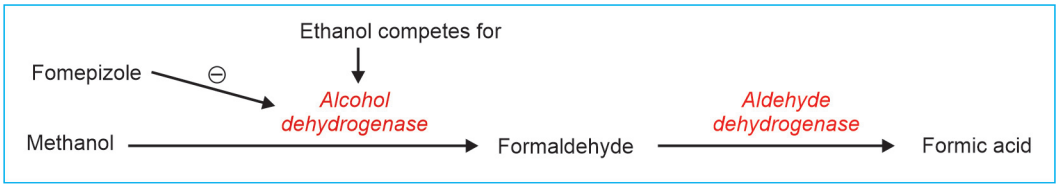


Fig. 18.2: Metabolism of methanol

It thus slows the metabolism of methanol and prevents the formation of toxic metabolites. A loading dose of 0.6 g/kg is followed by an infusion of 10 g/hour.

6. *Antidote:* **Fomepizole** specifically inhibits the enzyme alcohol dehydrogenase and thereby prevents the formation of toxic metabolites—formaldehyde and formic acid. Fomepizole is considered the antidote in methanol poisoning. It has the advantage over alcohol that it does not cause any intoxication by itself. Fomepizole is also effective in ethylene glycol poisoning.
7. *Haemodialysis:* Should be started at the earliest possible to enhance the removal of methanol.

Clinical Pharmacology

- Metabolised by zero order kinetics—blood alcohol levels rise disproportionately with higher doses.
- Microsomal enzyme inducer—related drug interactions are likely in chronic alcoholics.
- Therapeutic uses are limited; topically in bed sores—for astringent, antiseptic effects systemically in methanol poisoning.
- CNS depression additive with other drugs like sedative antihistamines, sedative hypnotics.
- Long-term use of 3–4 drinks per day can cause serious hepatotoxicity.
- Thiamine (vitamin B_1) should be administered to people consuming alcohol regularly to avoid Wernicke's and Korsakoff syndrome.
- Disulfiram, naltrexone may help in overcoming chronic alcohol dependence; metronidazole, sulfonylureas, griseofulvin, some cephalosporins, phenylbutazone and nitrofurantoin—also have disulfiram like effects.