22 Alcohols and Aldehydes

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Alcohols are carbon compounds containing hydroxyl groups (–OH). Alcohols are common types of chemicals, and exposure to alcohols can cause diverse biological effects, either indirectly through metabolic products or directly through the parent molecules. Ethanol, methanol, and isopropanol are the important alcohols due to their wide availability. These alcohols are able to induce toxicity both in animals and humans. Chemically, carbon chains with carbonyl groups (H–C=O) are classified as aldehydes. Among the aldehydes, formaldehyde is ubiquitously distributed in the environment. Human exposure to this chemical has received considerable attention due to its established carcinogenicity and developmental toxicity in laboratory animals. Accordingly, this chapter will focus on the clinical toxicology of ethanol, methanol, isopropanol, and formaldehyde.

22.1 ETHANOL

Ethanol (ethyl alcohol) has been produced from fermented grain, fruit juice, and honey for thousands of years. The presence of ethanol in wine, beer, and liquor and the use of it as a common solvent make it widely available to adults. The consumption and abuse of ethanol is not only a serious public health problem but also one of the major social problems, especially in Western countries.

22.1.1 Chemical Characteristics

Ethanol is a colorless aliphatic hydrocarbon molecule. This weakly polar molecule is both water and lipid soluble. The average apparent volume of distribution (V_d) of ethanol is about 0.6 l/kg, which is nearly equivalent to that of water. Ethanol diffuses across cell membranes easily and is absorbed from the gastrointestinal (GI) tract rapidly. As such, ethanol is able to distribute throughout the body. It penetrates the blood brain barrier and placenta and exerts its effects on most organ systems. Because oxidation of ethanol yields 7.1 kcal/g, sufficient calories can be obtained from ethanol alone for chronic drinkers if the daily intake of ethanol exceeds 5 g/kg of body weight. However, malnourishment can occur in chronic drinkers due to the absence of other important nutrients, which are present in a normal, complete diet.

22.1.2 Toxicokinetics

The absorption of ethanol from the GI tract is within 30 to 60 min after its ingestion. The stomach extracts about 20%, with the remainder of absorption occurring in the

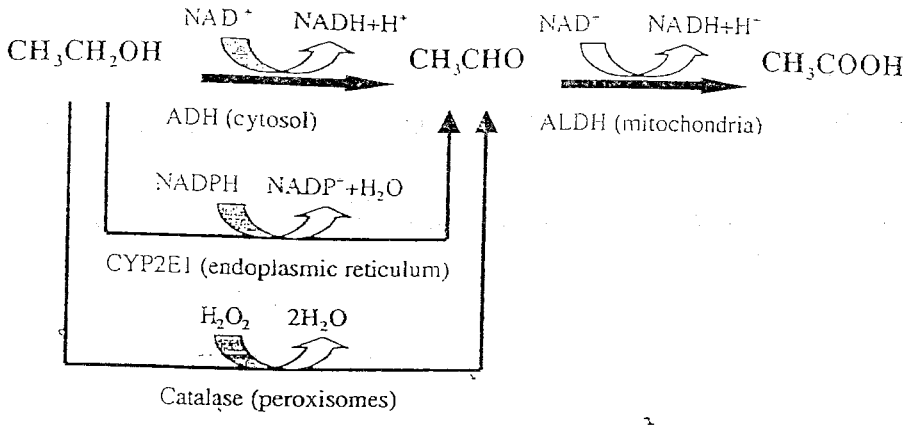

FIGURE 22.1 Metabolic pathways of ethanol.

small intestine. The absorption of ethanol from the GI tract may be delayed by various factors, including coingested food, drugs, and medical conditions that inhibit gastric emptying. After it enters the portal vein, ethanol first passes through the liver before it distributes to the rest of the body. More than 90% of the ingested ethanol is oxidized to acetaldehyde by liver and gastric mucosal cells; 5 to 10% is excreted unchanged by kidneys, lungs, and sweat. Oxidation of ethanol to acetaldehyde occurs predominantly in the liver by alcohol dehydrogenase (ADH). In addition, hepatic cytochrome P450, principally the isoform 2E1 (CYP2E1) in endoplasmic reticulum, and catalase in peroxisomes, are also able to catalyze the oxidation of ethanol to acetaldehyde. The acetaldehyde formed is further converted to acetate via the action of aldehyde dehydrogenase (ALDH) present in liver mitochondria (Figure 22.1).

Generally, women have a higher peak ethanol concentration than men if exposed to the same amount of ethanol, due to their lower body water content and the lower level of ADH in gastric mucosal cells. ADH, ALDH, and CYP2E1 exhibit genetic polymorphisms. Polymorphisms of these alcohol-metabolizing enzymes may lead to alterations in the ethanol elimination rate. For example, some Asian people have a facial flushing reaction when they drink alcohol, which is caused by the lower efficiency of their ALDH, leading to accumulated acetaldehyde in blood. In addition, polymorphisms of ethanol-metabolizing enzymes may influence the susceptibility to ethanol-induced diseases such as pancreatitis, liver cirrhosis and esophageal cancer. The average rate of ethanol metabolism in adults is 100 to 125 mg/kg/h in occasional drinkers, and can be up to 175 mg/kg/h in chronic drinkers. For medium-sized adults, the blood ethanol level drops at an average rate of 15 to 20 mg/dl/h.

22.1.3 Calculation of Blood Alcohol Concentrations (BAC)

Estimation of the blood concentrations of ethanol provides useful information regarding the severity of its intoxication. BAC can be calculated according to the following equation, where V_d is the apparent volume of distribution.

$$\text{BAC (mg/dl)} = [\text{amount of ethanol ingested (mg)}/V_d\ \text{(l/kg)}] \times \text{body weight (kg)} \times 10$$

22.1.4 Mechanisms of Toxicity

22.1.4.1 General Mechanisms of Toxicity

A multifactorial setting is responsible for the mechanisms of ethanol's toxic effects on individuals. The liver, nervous, gastrointestinal (GI), and cardiovascular (CV) systems are the principal targets of ethanol toxicity. Several cellular processes have been proposed to be crucially involved in ethanol-induced toxicity:

1. Ethanol directly affects cell membrane fluidity and modifies membrane proteins, which may result in alterations in the liquid-crystal state of membranes, membrane ion transport (i.e., Na^+ channel), transmembrane signal transduction (i.e., N-methyl-D-aspartate receptor), and activities of intrinsic membrane enzymes (i.e., Na^+-K^+-ATPase).
2. Recently, substantial evidence suggests that free radicals and reactive oxygen species (ROS) may contribute significantly to ethanol-induced toxicity. Metabolism of ethanol by microsomal enzymes, especially CYP2E1, has been shown to result in the formation of 1-hydroxyethyl radicals. Alternatively, induction of CYP2E1 by ethanol has been repeatedly demonstrated to lead to the increased production of ROS, including superoxide, hydrogen peroxide, and hydroxyl radicals. In this context, among various microsomal enzymes, CYP2E1 is an effective producer of ROS, possibly due to the high rate of electron leakage of the enzyme. The above reactive species, generated either from the metabolism of ethanol or the ethanol-induced CYP2E1, are able to attack important biomolecules, including lipids, proteins and nucleic acids, leading to oxidative cell injury.
3. Ethanol toxicity is also attributable to the formation of phosphatidylethanol (PE), a unique phospholipid formed in cell membranes in the presence of ethanol. The reaction is catalyzed by phospholipase D, an enzyme that normally catalyzes the hydrolysis of phospholipids, leading to the formation of phosphatidic acid. However, phospholipase D can also utilize ethanol as a substrate, resulting in the formation of the phosphatidylethanol. In view of the critical roles played by phospholipase D and phosphatidic acid in a number of cell signal transduction pathways, formation of phosphatidylethanol may be an important mechanism by which ethanol interferes with cell signaling, leading to cell dysfunction. In addition, the PE accumulated in membranes may also cause direct effects on the functions of cell membranes. Thus, both the inhibition of phospholipase D-mediated signal transduction and the accumulation of PE in membranes represent possible pathways through which ethanol may disturb cell function.
4. Fatty acid ethyl esters (FAEEs) produced from conjugations of ethanol and fatty acids are also implicated in ethanol-mediated toxicity in various organs, including heart, brain, pancreas, and liver. The synthesis of FAEEs from ethanol is catalyzed by FAEE synthase, a widely distributed enzyme. FAEEs have been shown to be cytotoxic species. Due to their lipophilicity,

FAEEs accumulate in cell membranes and are able to alter the properties of cell membranes and membrane-associated proteins. FAEEs may also accumulate in mitochondria, resulting in impaired mitochondrial oxidative phosphorylation.

5. Mitochondrial dysfunction is an important mechanism of ethanol-induced toxicity. Ethanol can change the permeability of inner mitochondrial membrane and may inhibit the expression of some components of the mitochondrial electron transport chain (METC), such as NADH dehydrogenase and cytochrome *c* oxidase, promoting ROS formation and resulting in decreased ATP synthesis. Moreover, ethanol may decrease mitochondrial glutathione levels and, as such, make them more vulnerable to the oxidative stress. ROS can cause damage to mitochondrial DNA and alteration of the METC, which further increases ROS production from the defective METC in the cells, leading to a vicious cycle of accumulating cell damage.

22.1.4.2 Mechanisms of Organ-Specific Toxicity

The liver is the most important target organ of ethanol-induced toxicity, especially chronic ethanol intoxication. The increased NADH level resulting from ethanol oxidation not only reduces gluconeogenesis but also accelerates triglyceride synthesis from free fatty acids, which leads to an accumulation of fat in the liver parenchyma. Ethanol stimulates release of endotoxin by Gram-negative bacteria in the gut, which has also been implicated in the ethanol-induced liver toxicity. Endotoxin is absorbed from the gut and enters the liver through the hepatic portal vein. Inside the liver, endotoxin activates Kupffer cells, resulting in release of the cytotoxic ROS and a number of cytokines, including tumor necrosis factor-α, interleukins, and prostaglandins. These cytokines can elicit inflammatory responses that may further lead to hepatic injury. Another mechanism of ethanol hepatotoxicity is through the formation of acetaldehyde. Acetaldehyde interacts with diverse cellular macromolecules, leading to the formation of protein adducts and enzyme inactivation. Moreover, acetaldehyde promotes GSH depletion, free-radical-mediated toxicity, and lipid peroxidation. Acetaldehyde has also been shown to stimulate collagen synthesis by liver stellate cells, which might be involved in the pathogenesis of ethanol-induced liver cirrhosis.

Central Nervous System (CNS) — Ethanol is a CNS depressant. Numerous different types of ion channels in CNS are important targets of ethanol, including ligand-gated, G-protein-regulated, and voltage-sensitive channels. The effects of ethanol on CNS are primarily attributed to the alteration of neurotransmission, including glutamate and GABA. Glutamate and GABA are major excitatory and inhibitory neurotransmitters in CNS. Acute ethanol exposure was shown to augment the GABA action at ligand-gated $GABA_A$ receptors. Excitatory glutamate receptors are classified into the NMDA and nonNMDA receptors. In addition to the activation of GABA receptors, ethanol inhibits the activation of NMDA glutamate receptors that are involved in cognition such as learning and memory.

Cardiovascular System — Ethanol-induced cardiotoxicity may involve several factors. Ethanol or its metabolite, acetaldehyde, may alter the myocardial stores of catecholamines and decrease the synthesis of cardiac contractile protein, leading to

a depression of myocardial contractility. Ethanol may also have adverse effects on cardiac conduction (i.e., prolonged QT interval and ventricular repolarization) and cause cardiac arrhythmias.

GI Tract — Ingestion of ethanol impairs the mucosal barrier directly and increases gastric and pancreatic secretion. In addition, FAEEs may play a major role in the disposition of ethanol in the pancreas and the development of pancreatitis. In this regard, the enzyme that catalyzes the formation of FAEEs (i.e., FAEE synthase), was found to have the highest activity in the pancreas.

22.1.5 Clinical Manifestations of Acute Toxicity

In the U.S., the level for ethanol intoxication is defined as 80 to 100 mg/dl in most of the states, and 400 mg/dl is the average lethal blood concentration. For chronic drinkers who become tolerant to the effects of ethanol, the corresponding concentrations to elicit the same degree of toxicity might be much higher than those for casual drinkers. The clinical manifestations of acute intoxication include sedation and relief of anxiety, reduced tension and coordination, impaired concentration and reaction time, tachycardia, and more severely, slurred speech, ataxia, and altered emotions. At high concentrations, it can cause breathing difficulties. Consumption of very large amounts of ethanol (>300 mg/dl) can produce metabolic and toxic coma that presents clinically as muscular hypotonia, respiratory depression, hypotension, and hypothermia. Clinical laboratory testing reveals hypoglycemia, ketosis, and electrolyte derangements in patients with severe ethanol intoxication.

22.1.6 Management of Acute Intoxication

The severity of acute alcohol intoxication is the basis for treatment, which is dependent on the blood ethanol concentration, the rising rapidity of ethanol level, and the duration of its high blood level. In the management of acute ethanol intoxication, the crucial goal is to prevent the severe respiratory depression and the pulmonary aspiration of vomitus that occurs. Respiratory and cardiovascular systems must be supported by protecting airway and establishing ventilatory and circulatory assistance. Glucose is administered to treat the hypoglycemia and ketosis. An electrolyte solution should be given to alcoholic patients who are vomiting and dehydrated. Severe vomiting causes the loss of potassium; thus supplementation of potassium is required if renal function is to remain normal. Moreover, for chronic drinkers, nutrients such as thiamine, folate, and magnesium should be given. Other strategies, including hemodialysis and gastric decontamination, have limited efficacy in the management of ethanol intoxication. Usually BAC falls at an average rate of 15 to 20 mg/dl/h. Most patients can recover with clinically supportive care.

22.1.7 Clinical Manifestations of Chronic Toxicity

Long-term consumption of ethanol impairs almost all of the organ systems (Table 22.1). It should be noted that alcoholics have a nearly two times higher risk of death than that of nondrinkers, due to alcoholic liver cirrhosis, infections, accidents, cancers, and cardiovascular diseases.

TABLE 22.1
Major Systemic Effects of Chronic Ethanol Consumption

Liver	Steatosis
	Alcoholic hepatitis
	Cirrhosis
	Liver cancer
Cardiovascular System	Alcoholic cardiomyopathy
	Cardiac arrhythmias
	Hypertension
Central Nervous System	Wernicke-Korsakoff syndrome
	Dementia
	Tolerance, dependence and withdrawal
Gastrointestinal System	Esophagitis
	Gastritis
	Malabsorption
	Pancreatitis
	Cancer of mouth, pharynx, and esophagus
Endocrine and Metabolic Systems	Hypoglycemia
	Alcoholic Ketoacidosis
	Hypomagnesemia
	Hypokalemia
	Malnutrition
	Gynecomastia
	Menstrual cycle abnormalities
Reproductive System	Hypogonadism
	Impotence
	Infertility
Hematologic System	Iron, folate, B_{12} deficiency anemias
	Leukopenia

Nervous System — Chronic use of ethanol profoundly affects the central and peripheral nervous system. Chronic alcoholic patients may be detected with damage to the frontal lobes of the brain, brain shrinkage, and an increase in the size of ventricles. Wernicke-Korsakoff syndrome resulting from alcohol abuse is classically characterized by a triad of paralysis of external eye muscles, cerebellar ataxia, and mental confusion, but the full clinical presentation is rarely encountered. It is thought to be associated with thiamine deficiency due to reduced thiamine (vitamin B1) absorption in alcoholics. Wernicke's encephalopathy is the acute phase of this disease, with longer duration of the confusional state in comparison to acute ethanol intoxication. Administration of thiamine alleviates the ataxia, ocular signs, and confusion; however, a memory deficit, known as Korsakoff psychosis, may be still present. Moreover, ethanol may cause bilateral and symmetrical visual impairment because of optic nerve degeneration.

Peripheral nerve damage is also an important characteristic of chronic ethanol intoxication. Ethanol-related neuropathy, especially when subclinical, seems to be frequent and mostly characterized by axonal degeneration of peripheral nerve fibers,

with earlier and more frequent involvement of sensory fibers and lower limbs. It usually begins with symmetrical paresthesias of hands and feet.

Liver — Liver disease is the most frequent clinical complication of chronic ethanol abuse. About 90% of chronic drinkers have fatty liver that is characterized by the abnormal accumulation of triglycerides in hepatocytes. While fatty liver is reversible, it may develop into alcoholic hepatitis, cirrhosis, or liver cancer. Alcoholic hepatitis refers to hepatocyte degeneration and necrosis. Clinically, patients may present with nausea, vomiting, jaundice, abdominal pain, and hepatosplenomegaly. Alcoholic cirrhosis, characterized by fibroblastic proliferation and the production of connective tissue in the periportal and centrilobular regions, is the most common type of cirrhosis in North America. The amount and the duration of ethanol consumption are highly correlated with the development of liver diseases. Moreover, concurrent infection with hepatitis B or C viruses aggravates the progress of liver diseases in alcoholics.

GI Tract — Long-term ingestion of ethanol increases the occurrence of gastritis and pancreatitis and causes intestine injury, leading to vitamin deficiencies, diarrhea, and loss of weight. In addition to liver cancer, alcoholism may also be associated with the development of cancer of the tongue, oral cavity, pharynx, larynx, or esophagus.

Cardiovascular System — Chronic heavy alcohol intake can result in dilated cardiomyopathy with ventricular hypertrophy and fibrosis. It may also induce atrial and ventricular arrhythmias. In addition, chronic consumption of ethanol, especially in large amounts, is associated with an increased incidence of hypertension.

Other Systems — Chronic alcoholics may also develop reproductive disorders, fluid disorders and electrolyte derangements, and hematologic disorders (Table 22.1). Alcoholics have a higher rate of infection, particularly respiratory infections (i.e., pneumonia and tuberculosis).

22.1.8 Management of Chronic Intoxication

The most common approach to prevent and treat ethanol-related diseases is to maintain abstinence by the administration of drugs that interfere with ethanol metabolism.

Disulfiram — Disulfiram (tetraethylthiuram) is the most commonly used drug to deter drinking. Disulfiram is an inhibitor of aldehyde dehydrogenase. It causes the accumulation of acetaldehyde, which elicits extreme discomfort soon after the intake of ethanol, including flushing, throbbing, headache, nausea, vomiting, sweating, hypotension, and confusion. Although disulfiram is rapidly absorbed, it has little effect in nondrinkers. It takes about 12 h to exert its full effect. This drug is long-lasting (a few days) due to its slow elimination. Administration of disulfiram should begin at least 24 h after patients have been free of ethanol. Disulfiram inhibits the metabolism of other therapeutic agents such as phenytoin, isoniazid, and oral anticoagulants. Compliance is often a problem with disulfiram treatment. Additionally, the drug may influence liver function and cause mild alterations in liver function tests. Due to poor compliance and side effects, disulfiram is becoming less favored in alcoholism therapy.

Naltrexone — Naltexone works as an opioid receptor antagonist with high oral availability and a long duration of action. It was approved by the FDA for alcoholism treatment in 1994. Animal research and clinical experience indicate that there is a link between alcohol consumption and opioids. Opioids may increase the craving for ethanol, while opioid receptor antagonists can reduce the urge to drink and decrease ethanol intake. Typically, naltrexone should be administrated in conjunction with psychosocial therapy. The major side effects of naltrexone are nausea, dizziness, and headache. These appear more commonly in women than in men. Considering that an overdose of naltrexone can cause severe liver damage, acute hepatitis and liver failure are contraindications of naltrexone administration. In contrast to disulfiram, naltrexone has good compliance in alcoholism therapy. Due to the potential hepatotoxicity for both drugs, the combination of naltrexone and disulfiram should be avoided.

Nalmefene — Nalmefene is a promising opioid antagonist in preliminary clinical tests. It has some advantages over naltrexone, including greater oral availability, longer duration of action, and lack of dose-dependent liver toxicity.

Other Drugs — In addition to the opioid system, the glutamate, serotonergic, and dopaminergic neurotransmitter systems might be also involved in the regulation of ethanol consumption. For example, acamprosate, a competitive inhibitor of the NMDA receptor, can decrease the rate of relapse and enhance the duration of abstinence. Buspirone, a serotonin receptor antagonist, fluoxetine, a serotonin reuptake inhibitor, and antagonists of D1 and D2 dopamine receptors are being studied as new agents for treating alcoholism. In addition to pharmacotherapy, magnesium, potassium phosphate, multivitamins, and folate should be administrated to alcoholics to correct the hypomagnesemia, hypophosphatemia, hypokalemia, and vitamin deficiency associated with chronic alcohol abuse.

22.1.9 Fetal Alcohol Syndrome (FAS)

FAS is the most common preventable cause of mental retardation and congenital malformation in humans. It is estimated that FAS affects 4000 infants per year in the U.S., and an additional 7000 cases show fetal alcohol effects. The typical features of FAS include retarded body growth, craniofacial abnormalities, and CNS dysfunction. The mechanism underlying the teratogenic effects caused by chronic ethanol abuse remains uncertain.

22.1.10 Tolerance, Dependence, and Withdrawal

Tolerance refers to the situation where a higher dose of ethanol is required to elicit the same behavioral or physiological response. **Dependence** is defined as a compulsive desire to avoid the appearance of withdrawal syndrome when ethanol ingestion is ceased. **Withdrawal syndrome** consists of sleep disruption, anxiety, sweating, tremors, even seizures and hallucinations. It is thought that the development of tolerance to ethanol involves complex mechanisms and occurs in part via the induction of alcohol-metabolizing enzymes. Downregulation of the GABA-mediated response and upregulation of NMDA receptor function appear to account for the CNS hyperexcitability in ethanol withdrawal.

22.1.11 Methods of Detection

To detect and quantify ethanol, many methods have been established. Blood alcohol levels can be determined accurately by immunoassay or gas chromatography in most hospitals, but it takes longer to obtain these results than from other methods. An electrochemical meter has been applied to test alcohol concentration in venous blood, and this method has high sensitivity but poor specificity. Breath alcohol analyzers are widely used as alcohol screening tools, especially by law-enforcement agencies. This test is performed by microprocessors and infrared spectral analysis with good accuracy and precision. To sample the breath of unconscious patients, breath-alcohol devices with mouth cups and nasal tubes should be used. Another method to determine ethanol exposure is the fatty acid ethyl esters (FAEEs) test. This test is highly sensitive and works as a hallmark of recent ethanol use since FAEEs can be detected even after ethanol is completely metabolized.

22.2 METHANOL

Methanol (methyl alcohol) is readily available at variable concentrations in numerous industrial and household products, including windshield washer fluid. It is also used in the manufacture of formaldehyde and methyl tert-butyl ether. Exposure to methanol commonly occurs in the workplace and household. In addition, methanol may be intentionally ingested by alcoholics.

22.2.1 Toxicokinetics

Methanol is absorbed via the skin, GI, and respiratory routes. When ingested, peak levels of methanol in blood occur within 30 to 60 min. Methanol is oxidized to formaldehyde by ADH in liver, which in turn is converted to formate via the action of formaldehyde dehydrogenase. Formation of formate is largely responsible for the toxicity of methanol. Formate can be eliminated by formyl-tetrahydrofolate-synthetase (formyl-THF-synthetase) by combining with tetrahydrofolate (THF) to form 10-formyl-THF. This is then converted to carbon dioxide by the catalytic action of formyl-THF-dehydrogenase (F-THF-DH). The elimination half-life of formate is about 3.5 h. Ethanol and the ADH inhibitor, fomepizole can competitively inhibit the metabolism of methanol by ADH, thus delaying its elimination. The metabolic pathway of methanol is illustrated in Figure 22.2.

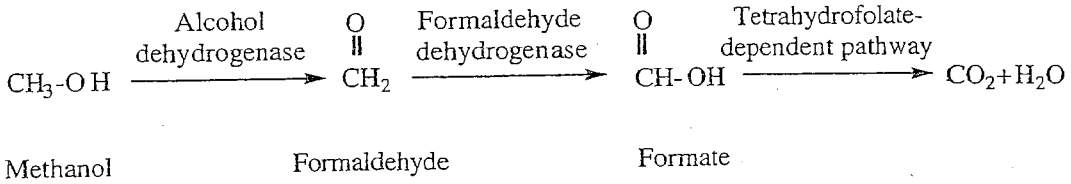

FIGURE 22.2 Metabolism of methanol.

22.2.2 Mechanisms of Toxicity

Most of the toxic effects of methanol are attributed to the formation of formate. Formate inhibits the mitochondrial cytochrome *c* oxidase complex and concomitantly decreases ATP production, resulting in increased anaerobic glycolysis and production of lactate. The accumulation of formate and lactate causes systemic acidosis, which facilitates the formation of nonionized formate, leading to its increased cellular accumulation and cytotoxic effects. In addition, production of hydroxyl radicals and induction of lipid peroxidation may also be implicated in the cellular damage induced by methanol intoxication. Ocular tissues such as optic nerve and retina are more susceptible to the toxicity of formate, probably because the retina is able to metabolize methanol to formate. Histologically, the optic nerve and retina edema occurs in methanol intoxication.

22.2.3 Clinical Manifestations of Acute Intoxication

Methanol primarily affects the nervous, ocular, and GI systems. While intoxication symptoms appear within a few hours after methanol intake, they can be delayed more than 30 h due to varied individual response and/or coingestion of ethanol.

Ocular — Among the symptoms induced by methanol, the most typical clinical presentation is visual disturbance, including blurred vision, visual hallucination, and even visual loss. Upon eye examinations, retinal edema, visual field constriction, and nonreactive pupils might be found in patients.

Nervous System — Methanol may elicit various and nonspecific neurological manifestations, such as headache, dizziness, bradycardia, impaired consciousness, seizures, and even coma.

Others — Methanol-mediated effects on the GI system may include abdominal pain, diarrhea, GI hemorrhage, and pancreatitis. Systemic acidosis induced by methanol intoxication may also increase the respiratory rate and cause Kussmaul respiration in severe cases.

22.2.4 Management of Acute Intoxication

General Supportive Care — Respiratory support, cardiac monitoring and circulatory assistance should be established. Sedative agents such as phenobarbital should be administrated to patients with seizures.

Antidote Therapy — Ethanol and the ADH inhibitor, fomepizole, are used as antidotes in methanol intoxication. They effectively block the metabolism of methanol and reduce its toxic effects. As such, the antidote should be given i.v. to all patients with methanol intoxication. The use of ethanol may cause CNS depression and hypoglycemia, and its dose is not easily manipulated. However, fomepizole has great efficacy and fewer side effects than ethanol; hence it is the favored antidote in the treatment of methanol intoxication.

Correction of Acidosis — Sodium bicarbonate may be administrated i.v. to ameliorate metabolic acidosis, especially in severe cases.

Others — If the blood concentration of methanol is higher than 50 mg/dl, hemodialysis should be carried out to enhance its elimination. Moreover, folinic acid (leucovorin) can be given i.v. to facilitate the elimination of formate.

22.3 ISOPROPANOL

Isopropanol (isopropyl alcohol) is a colorless and volatile alcohol with fruity odor and a slight bitter taste. It is present in rubbing alcohol, industrial solvents, paints, disinfectants, and drugs. It may be ingested accidentally by nonalcoholics and intentionally by alcoholics.

22.3.1 Toxicokinetics

Isopropanol can enter the body by ingestion, inhalation of the vapors, or through the skin. GI absorption is a major route of exposure leading to toxicity, while inhalational or dermal absorption may also elicit toxic effects. Blood isopropanol reaches peak levels 30 min after ingestion. It is metabolized by hepatic ADH, and 80% is converted to acetone (Figure 22.3). Acetone is excreted primarily through the renal route (20% being excreted unchanged), and a small amount through lungs, saliva, and gastric juices. The range of elimination half-life for isopropanol is 2.5 to 6.6 h and 10 to 31 h for acetone. Because acetone cannot be further converted to an acid, isopropanol intoxication is not considered to cause metabolic acidosis.

22.3.2 Mechanisms of Toxicity

Studies on mechanisms of isopropanol-induced toxicity are lacking in the literature. The principal toxic effect of isopropanol is CNS depression that is twice as potent as ethanol. In this context, acetone, the by-product of isopropanol, is a potent central nervous system depressant.

22.3.3 Clinical Manifestations of Acute Toxicity

The presentation of CNS depression with isopropanol intoxication includes inebriation with drowsiness, poor balance, staggering gait, slurred speech, and poor coordination, as well as sweating, stupor, coma, and even death due to respiratory depression. GI responses such as nausea, vomiting, and abdominal pain and hemorrhage into the bronchi and the chest cavity may occur. In addition, the patient may have a distinct odor of acetone. In severe intoxication, CV compromise may occur, including myocardial depression and severe hypotension. Less common presentations include renal tubular necrosis, hemolytic anemia, acute myopathy, and hypothermia. For young children with isopropanol ingestion, irritability, hypotonia, and seizures may be indicators of intoxication.

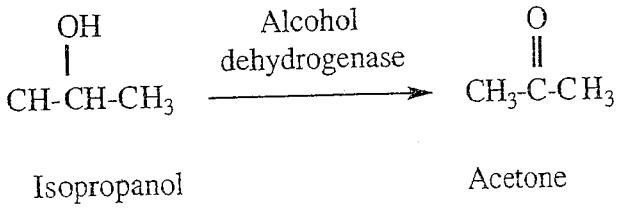

FIGURE 22.3 Metabolism of isopropanol.

22.3.4 Management of Acute Intoxication

Respiratory support and cardiac monitoring are required in the treatment of isopropanol toxicity. For respiratory depressed patients, endotracheal intubation and ventilatory support should be applied. For severe intoxication, gastric lavage and hemodialysis may be useful to remove the isopropanol.

22.4 FORMALDEHYDE

Formaldehyde is a nearly colorless gas with a pungent odor. It dissolves easily in water and is found in formalin (a formaldehyde solution containing water) and methanol (wood alcohol). Formaldehyde is used as a preservative, a hardening and reducing agent, a corrosion inhibitor, and a sterilizing agent. It is also found in glues, pressed wood products, foam insulation, and a wide variety of molded or extruded plastic items. Indoor sources include permanent press fabrics, carpets, pesticide formulations, and cardboard and paper products. Outdoor sources include emissions from fuel combustion, oil refining processes, and environmental tobacco smoke.

22.4.1 Toxicokinetics

Formaldehyde can enter the body by inhalation, ingestion, or skin contact. Formaldehyde is readily absorbed via the respiratory and GI routes. Dermal absorption of formaldehyde appears to be very slight. Absorbed formaldehyde is metabolized quickly to formate by a glutathione-dependent formaldehyde dehydrogenase. Formate can either be further converted to carbon dioxide as described in Section 22.2.1 or can enter the one-carbon cycle, incorporated as a methyl group into nucleic acids and proteins. Metabolites of formaldehyde are mainly excreted through respiratory and renal routes.

22.4.2 Mechanisms of Toxicity

Formaldehyde can cause multiorgan toxicity upon either acute or chronic exposure. Acute toxicity is largely attributable to its irritating and corrosive properties. The mechanisms underlying formaldehyde-induced chronic toxicity remain to be elucidated. The binding of formaldehyde to endogenous proteins may result in the formation of neoantigens. Such neoantigens may elicit an immune response that might account for the occurrence of asthma and other health complaints associated with formaldehyde exposure. In this regard, long-term exposure to formaldehyde is associated with the formation of formaldehyde-albumin adducts, autoantibodies, and immune activation in patients occupationally exposed, or residents of mobile homes or homes containing particleboard sub-flooring. In addition, formaldehyde has been shown to cause cancer, especially nasal cancer in laboratory animals. The carcinogenicity of formaldehyde may be due to its high reactivity with DNA. However, its carcinogenicity in humans remains to be established. Formaldehyde may also cause genotoxicity in humans. For example, a higher frequency of the DNA-protein crosslinks (DPCs) and sister chromatid exchanges (SCEs) was observed in peripheral-blood lymphocytes of workers occupationally exposed to formaldehyde, as

compared to unexposed workers. It appears unlikely that formaldehyde reaches concentrations sufficient to cause reproductive and developmental damages in humans, due to its rapid metabolism.

22.4.3 Clinical Manifestations of Acute Intoxication

Formaldehyde primarily affects the mucous membranes of the upper airways and eyes. The manifestations include watery eyes, burning sensations in the eyes and throat, nausea, wheezing, coughing, chest tightness, and difficulty in breathing at elevated levels (above 0.1 ppm). Drinking formalin can cause severe burns to the throat and stomach, and as little as 30 ml of formalin can cause death.

22.4.4 Management of Acute Intoxication

There is no antidote for formaldehyde poisoning. Supportive care constitutes the primary management of patients with acute formaldehyde intoxication. With supportive care, most patients fully recover.

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