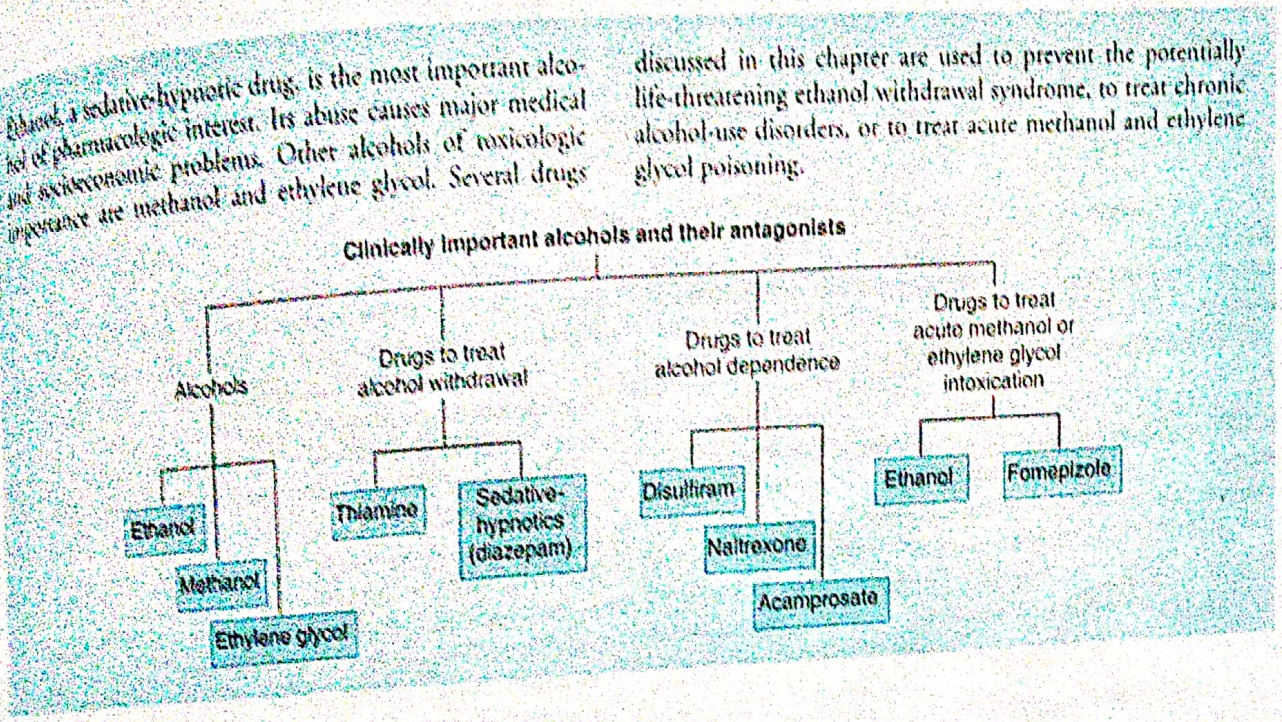
CHAPTER

23

Alcohols

Ethanol, a sedative-hypnotic drug, is the most important alcohol of pharmacologic interest. Its abuse causes major medical and socioeconomic problems. Other alcohols of toxicologic importance are methanol and ethylene glycol. Several drugs discussed in this chapter are used to prevent the potentially life-threatening ethanol withdrawal syndrome, to treat chronic alcohol-use disorders, or to treat acute methanol and ethylene glycol poisoning.



ETHANOL

A. Pharmacokinetics

After ingestion, ethanol is rapidly and completely absorbed; the drug is then distributed to most body tissues. Two enzyme systems metabolize ethanol to acetaldehyde (Figure 23–1).

1. Alcohol dehydrogenase (ADH)—This family of cytosolic, NAD^+-dependent enzymes, found mainly in the liver and gut, accounts for the metabolism of low to moderate doses of ethanol. Because of the limited supply of the coenzyme NAD^+, the reaction has *zero-order kinetics*, resulting in a fixed capacity for ethanol metabolism of 7–10 g/h. Gastrointestinal metabolism of ethanol is lower in women than in men. Genetic variation in ADH affects the rate of ethanol metabolism and vulnerability to alcohol-use disorders.

2. Microsomal ethanol-oxidizing system (MEOS)—At blood ethanol levels higher than 100 mg/dL, the liver microsomal mixed function oxidase system that catalyzes most phase I drug-metabolizing reactions (see Chapter 2) contributes significantly to ethanol metabolism (Figure 23–1). Chronic ethanol consumption induces cytochrome P450 enzyme synthesis and MEOS activity; this is partially responsible for the development of tolerance to ethanol. The primary isoform of cytochrome P450 induced by ethanol—2E1 (see Table 4–3)—converts acetaminophen to a hepatotoxic metabolite.

Acetaldehyde formed from the oxidation of ethanol by either ADH or MEOS is rapidly metabolized to acetate by aldehyde dehydrogenase, a mitochondrial enzyme found in the liver and many other tissues. Aldehyde dehydrogenase is inhibited by **disulfiram** and other drugs, including **metronidazole, oral hypoglycemics,** and some **cephalosporins.** Some individuals, primarily of Asian descent, have genetic deficiency of aldehyde dehydrogenase.

High-Yield Terms to Learn

Alcohol abuse	An alcohol-use disorder characterized by compulsive use of ethanol in dangerous situations (eg, driving, combined with other CNS depressants) or despite adverse consequences directly related to the drinking
Alcohol dependence	An alcohol-use disorder characterized by alcohol abuse plus physical dependence on ethanol
Alcohol withdrawal syndrome	The characteristic syndrome of insomnia, tremor, agitation, seizures, and autonomic instability engendered by deprivation in an individual who is physically dependent on ethanol
Delirium tremens (DTs)	Severe form of alcohol withdrawal whose main symptoms are sweating, tremor, confusion, and hallucinations
Fetal alcohol syndrome	A syndrome of craniofacial dysmorphia, heart defects, and mental retardation caused by the teratogenic effects of ethanol consumption during pregnancy
Wernicke-Korsakoff syndrome	A syndrome of ataxia, confusion, and paralysis of the extraocular muscles that is associated with chronic alcoholism and thiamine deficiency

After consumption of even small quantities of ethanol, these individuals experience nausea and a flushing reaction from accumulation of acetaldehyde.

B. Acute Effects

1. CNS—The major acute effects of ethanol on the CNS are sedation, loss of inhibition, impaired judgment, slurred speech, and ataxia. In nontolerant persons, impairment of driving ability is thought to occur at ethanol blood levels between 60 and 80 mg/dL. Blood levels of 120 to 160 mg/dL are usually associated with gross drunkenness. Levels greater than 300 mg/dL may lead to loss of consciousness, anesthesia, and coma sometimes with fatal respiratory and cardiovascular depression. Blood levels higher than 500 mg/dL are usually lethal. Individuals with alcohol dependence who are tolerant to the effects of ethanol can function almost normally at much higher blood concentrations than occasional drinkers. Additive CNS depression occurs with concomitant ingestion of ethanol and a wide variety of CNS depressants, including sedative-hypnotics, opioid agonists, and many drugs that block muscarinic and H_1 histamine receptors. The molecular mechanisms underlying the complex CNS effects of ethanol are not fully understood. Specific receptors for ethanol have not been identified. Rather, ethanol appears to modulate the function of a number of signaling proteins. It facilitates the action of GABA at $GABA_A$ receptors, inhibits the ability of glutamate to activate NMDA (*N*-methyl-D-aspartate) receptors, and modifies the activities of adenylyl cyclase, phospholipase C, and ion channels.

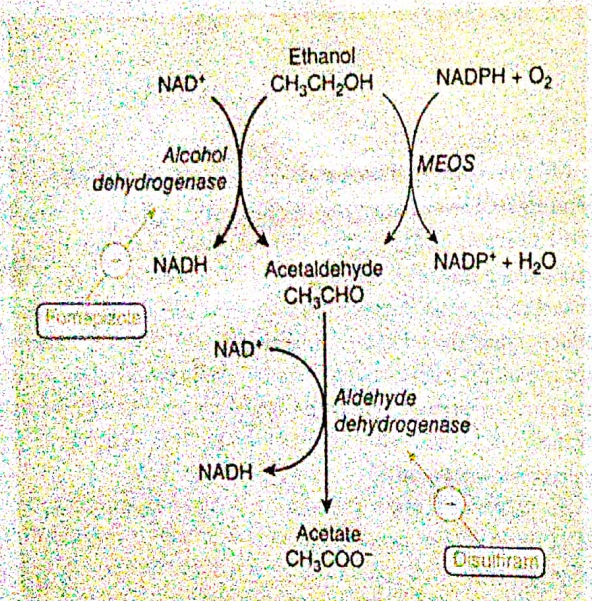


FIGURE 23–1 Metabolism of ethanol by alcohol dehydrogenase (ADH) and the microsomal ethanol-oxidizing system (MEOS). Alcohol dehydrogenase and aldehyde dehydrogenase are inhibited by fomepizole and disulfiram, respectively. (Reproduced, with permission, from Katzung BG, Masters SB, Trevor AT, editors: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 23–1.)

2. Other organ systems—Ethanol, even at relatively low blood concentrations, significantly depresses the heart. Vascular smooth muscle is relaxed, which leads to vasodilation, sometimes with marked hypothermia.

C. Chronic Effects

1. Tolerance and dependence—Tolerance occurs mainly as a result of CNS adaptation and to a lesser extent by an increased rate of ethanol metabolism. There is cross-tolerance to sedative-hypnotic drugs that facilitate GABA activity (eg, benzodiazepines and barbiturates). Both psychological and physical dependence are marked.

2. Liver—Liver disease is the most common medical complication of chronic alcohol abuse. Progressive loss of liver function occurs with reversible fatty liver progressing to irreversible hepatitis, cirrhosis, and liver failure. Hepatic dysfunction is often more severe in women than in men and in both men and women infected with hepatitis B or C virus.

3. Gastrointestinal system—Irritation, inflammation, bleeding, and scarring of the gut wall occur after chronic heavy use of ethanol and may cause absorption defects and exacerbate nutritional deficiencies. Chronic alcohol abuse greatly increases the risk of pancreatitis.

4. CNS—Peripheral neuropathy is the most common neurologic abnormality in chronic alcohol abuse. More rarely, thiamine deficiency, along with alcohol abuse, leads to **Wernicke-Korsakoff** syndrome, which is characterized by ataxia, confusion, and paralysis of the extraocular muscles. Prompt treatment with parenteral thiamine is essential to prevent a permanent memory disorder known as Korsakoff's psychosis.

5. Endocrine system—Gynecomastia, testicular atrophy, and salt retention can occur, partly because of altered steroid metabolism in the cirrhotic liver.

6. Cardiovascular system—Excessive chronic ethanol use is associated with an increased incidence of hypertension, anemia, and dilated cardiomyopathy. Acute drinking for several days ("binge" drinking) can cause arrhythmias. However, the ingestion of modest quantities of ethanol (10–15 g/day) raises serum levels of high-density lipoprotein (HDL) cholesterol and may *protect* against coronary heart disease.

7. Fetal alcohol syndrome—Ethanol use in pregnancy is associated with teratogenic effects that include mental retardation (most common), growth deficiencies, microcephaly, and a characteristic underdevelopment of the midface region.

8. Neoplasia—Ethanol is not a primary carcinogen, but its chronic use is associated with an increased incidence of neoplastic diseases in the gastrointestinal tract and a small increase in the risk of breast cancer.

9. Immune system—Chronic alcohol abuse has complex effects on immune functions because it enhances inflammation in the liver and pancreas and inhibits immune function in other tissues. Heavy use predisposes to infectious pneumonia.

SKILL KEEPER: ELIMINATION HALF-LIFE (SEE CHAPTER 1)

Search "high and low" through drug information resources and you will not find data on the elimination half-life of ethanol! Can you explain why this is the case? The Skill Keeper Answer appears at the end of the chapter.

D. Treatment of Acute and Chronic Alcoholism

1. Excessive CNS depression—Acute ethanol intoxication is managed by maintenance of vital signs. Prevention of aspiration after vomiting. Intravenous dextrose is standard. Thiamine administration is used to protect against Wernicke-Korsakoff syndrome, and correction of electrolyte imbalance may be required.

2. Alcohol withdrawal syndrome—In individuals physically dependent on ethanol, discontinuance can lead to a withdrawal syndrome characterized by insomnia, tremor, anxiety, and, in severe cases, life-threatening seizures and delirium tremens (DTs). Peripheral effects include nausea, vomiting, diarrhea, and arrhythmias. The withdrawal syndrome is managed by correction of electrolyte imbalance, and administration of thiamine and a sedative-hypnotic. A long-acting benzodiazepine (eg, diazepam, chlordiazepoxide) is preferred unless the patient has compromised liver function, in which case a short-acting benzodiazepine with less complex metabolism (eg, lorazepam) is preferred.

3. Treatment of alcoholism—Alcoholism is a complex sociomedical problem, characterized by a high relapse rate. Several CNS neurotransmitter systems appear to be targets for drugs that reduce the craving for alcohol. The opioid receptor antagonist **naltrexone** has proved to be useful in some patients, presumably through its ability to decrease the effects of endogenous opioid peptides in the brain (see Chapters 31 and 32). **Acamprosate,** an NMDA glutamate receptor antagonist, is also FDA approved for treatment of alcoholism. The aldehyde dehydrogenase inhibitor disulfiram is used adjunctively in some treatment programs. If ethanol is consumed by a patient who has taken **disulfiram,** acetaldehyde accumulation leads to nausea, headache, flushing, and hypotension (Figure 23–1).

OTHER ALCOHOLS

A. Methanol

Methanol (wood alcohol), a constituent of windshield cleaners and "canned heat," is sometimes ingested intentionally. Intoxication causes visual dysfunction, gastrointestinal distress, shortness of breath, loss of consciousness, and coma. Methanol is metabolized to formaldehyde and formic acid, which causes severe acidosis, retinal damage, and blindness. The formation of formaldehyde is reduced by prompt intravenous administration of **fomepizole,** an inhibitor of alcohol dehydrogenase, or ethanol, which competitively inhibits alcohol dehydrogenase oxidation of methanol (Figure 23–2).

B. Ethylene Glycol

Industrial exposure to ethylene glycol (by inhalation or skin absorption) or self-administration (eg, by drinking antifreeze products) leads to severe acidosis and renal damage from the metabolism of ethylene glycol to oxalic acid. Prompt treatment with intravenous fomepizole or ethanol may slow or prevent formation of this toxic metabolite (Figure 23–2).

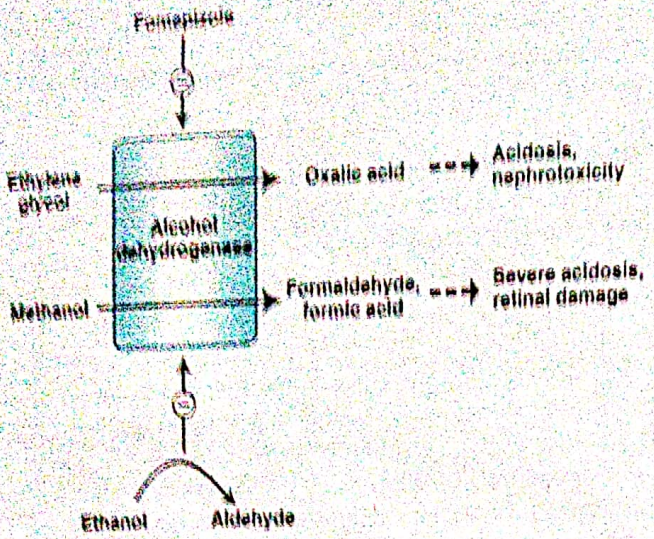


FIGURE 23–2 The oxidation of ethylene glycol and methanol by alcohol dehydrogenase (ADH) creates metabolites that cause serious toxicity. Fomepizole, an inhibitor of alcohol dehydrogenase, is used in methanol or ethylene glycol poisoning to slow the rate of formation of toxic metabolites. Ethanol, a substrate with higher affinity for ADH than ethylene glycol or methanol, also slows the formation of toxic metabolites and is an alternative to fomepizole.

QUESTIONS

1. A 45-year-old moderately obese man has been drinking heavily for 72 h. This level of drinking is much higher than his regular habit of drinking 1 alcoholic drink per day. His only significant medical problem is mild hypertension, which is adequately controlled by metoprolol. With this history, this man is at significant risk for
   (A) Arrhythmia
   (B) Bacterial pneumonia
   (C) Hyperthermia
   (D) Tonic-clonic seizures
   (E) Wernicke-Korsakoff syndrome

2. A 42-year-old man with a history of alcoholism is brought to the emergency department in a confused and delirious state. He has truncal ataxia and ophthalmoplegia. The most appropriate immediate course of action is to administer diazepam plus
   (A) Chlordiazepoxide
   (B) Disulfiram
   (C) Folic acid
   (D) Fomepizole
   (E) Thiamine

3. The cytochrome P450-dependent microsomal ethanol oxidizing system (MEOS) pathway of ethanol metabolism is *most* likely to be maximally activated under the condition of low concentrations of
   (A) Acetaldehyde
   (B) Ethanol
   (C) NAD^+
   (D) NADPH
   (E) Oxygen

4. A freshman student (weight 70 kg) attends a college party where he rapidly consumes a quantity of an alcoholic beverage that results in a blood level of 500 mg/dL. Assuming the young man has not had an opportunity to develop tolerance to ethanol, his present condition is *best* characterized as
   (A) Able to walk, but not in a straight line
   (B) Alert and competent to drive a car
   (C) Comatose and near death
   (D) Sedated with increased reaction times
   (E) Slightly inebriated

Questions 5 and 6. A homeless middle-aged male patient presents in the emergency department in a state of intoxication. He is noted to be behaviorally disinhibited and rowdy. He admits that he has recently consumed about a pint of a red-colored liquid that his friends were using to "get high." He complains that his vision is blurred and that it is "like being in a snowstorm." His breath smells a bit like formaldehyde. He is acidotic.

5. Which of the following is the most likely cause of the patient's intoxicated state?
   (A) Ethanol
   (B) Ethylene glycol
   (C) Isopropanol
   (D) Hexane
   (E) Methanol

6. After assessing and stabilizing the patient's airway, respiratory and circulatory status, fomepizole was administered intravenously. Which of the following most accurately describes the therapeutic purpose of the fomepizole administration?
   (A) Accelerate the rate of elimination of the toxic liquid he consumed
   (B) Combat his acidosis
   (C) Inhibit the metabolic production of a toxic metabolite of the poison
   (D) Prevent alcohol withdrawal seizures
   (E) Sedate the patient

7. The regular ingestion of moderate or heavy amounts of alcohol predisposes to hepatic damage after overdose of acetaminophen because of chronic ethanol ingestion
   (A) Blocks acetaminophen metabolism
   (B) Causes thiamine deficiency
   (C) Displaces acetaminophen from plasma proteins
   (D) Induces liver drug-metabolizing enzymes
   (E) Inhibits renal clearance of acetaminophen

8. A 23-year-old pregnant woman with alcoholism presents to the emergency department in the early stages of labor. She had consumed large amounts of alcohol throughout her pregnancy. This patient's infant is at high risk of a syndrome that includes
   (A) Ambiguous genitalia in a male fetus and normal genitalia in a female fetus
   (B) Failure of closure of the atrial septum or ventricular septum
   (C) Limb or digit malformation
   (D) Mental retardation and craniofacial abnormalities
   (E) Underdevelopment of the lungs