CHAPTER 103

Toxic Alcohols

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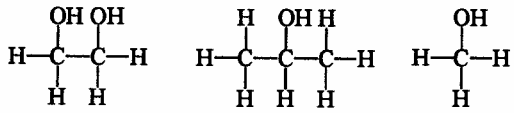


Ethylene Glycol
MW = 62 Daltons
Isopropanol
MW = 60 Daltons
Methanol
MW = 32 Daltons

A 56-year-old man was brought to the hospital by ambulance after being found unresponsive by his family. A can of "antifreeze" was also brought. The patient had a history of diabetes mellitus for which he was taking rosiglitazone. He had appeared normal when he was last seen, several hours prior to arrival. The family reported that he had been upset after losing his job. Upon initial evaluation, the patient was unresponsive to verbal stimuli, but withdrew to pain. There was no sign of trauma. Initial vital signs were: blood pressure, 99/56 mm Hg; pulse, 68 beats/min; respirations, 18 breaths/min; and temperature 98.4°F (36.9°C). Pulse oximetry revealed a saturation of 100% on room air, and rapid bedside glucose was 114 mg/dL by fingerstick. Pupils were 4 mm, equal, and reactive to light, and a funduscopic examination was normal. A gag reflex was present. Mucous membranes were moist, the lungs were clear to percussion and auscultation, and a cardiac examination was normal. Bowel sounds were present, the bladder was not distended, the skin was warm and dry with no lesions, and there was no clubbing, cyanosis, or edema of the extremities. The neurologic examination was notable for a depressed level of consciousness, but was otherwise without focal findings.

An intravenous line was established with 0.9% NaCl solution, and the patient was attached to a cardiac monitor. Empiric thiamine and naloxone were administered with no response. A screening electrocardiogram was normal. An arterial blood gas revealed a metabolic acidosis with respiratory compensation: pH 7.39; PCO_2, 32 mm Hg; PO_2, 94 mm Hg. The blood lactate concentration was 0.7 mEq/L. Serum electrolytes were Na^+, 140 mEq/L; K^+, 3.8 mEq/L; CL^-, 108 mEq/L; HCO_3^-, 16 mEq/L; Ca^{2+}, 8.8 mEq/L. Other significant laboratory values were BUN, 16 mg/dL; creatinine, 1.2 mg/dL; glucose 116 mg/dL; ethanol 0 mg/dL; urine ketones, negative; measured serum osmolality, 421 mOsm/kg. Acetaminophen and salicylates were undetectable. The calculated anion gap was 16 mEq/L and the calculated osmolarity was 292 mOsm/L, giving an osmol gap of 129 mOsm. The urine was examined with a Woods lamp and did not fluoresce; the sediment did not contain any crystals.

The patient was treated with fomepizole (15 mg/kg IV, followed by 10 mg/kg every 12 hours), thiamine (100 mg IV every 6 hours), folate (50 mg IV every 6 hours), and pyridoxine (50 mg IV every 6 hours). He was admitted to the medical intensive care unit (ICU), and nephrology consultation requested for hemodialysis. The patient was dialyzed for 4 hours. Initial toxic alcohol levels had not been requested, but the initial blood sample was later recovered and sent for analysis. In the serum, ethylene glycol and isopropanol were undetectable and the serum methanol was 95 mg/dL. Fomepizole and folate were continued after hemodialysis, and a repeat methanol level was 119 mg/dL. The patient was dialyzed again, with a subsequent methanol level of 72 mg/dL. At this point (about 48 hours after presentation), his mental status had gradually returned to normal. The fomepizole dose was increased to 15 mg/kg every 12 hours. After a third course of hemodialysis, the methanol level was 23 mg/dL, and therapy was discontinued except for folate. The patient was transferred to the psychiatry ward for further evaluation. The can brought with the patient by the family contained automotive "gas line antifreeze."

CHEMISTRY

Alcohols are hydrocarbons that contain a *hydroxyl* (-OH) group. The term *toxic alcohols* traditionally refers to alcohols other than ethanol, that is, those alcohols not intended for ingestion. In a sense, this is arbitrary, because all alcohols are toxic, causing inebriation and end-organ effects, such as hepatic effects, in the case of ethanol. The most common toxic alcohols encountered clinically are methanol and ethylene glycol (1,2-ethanediol). Ethylene glycol contains 2 hydroxyl groups; molecules with this characteristic are

termed *diols* (also known as *glycols* because these molecules generally have a sweet taste). Other common toxic alcohols include isopropanol (or isopropyl alcohol or 2-propanol), benzyl alcohol (phenylmethanol), and propylene glycol (1,3-propanediol). *Primary* alcohols, such as methanol and ethanol, contain a hydroxyl group on the end of the molecule (the *terminal* carbon), whereas *secondary* alcohols, such as isopropanol, contain hydroxyl groups bound to nonterminal carbons.

Glycol ethers are glycols with a hydrocarbon chain bound to one or more of the hydroxyl groups (forming the basic structure $R_1O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}R_2$ or $R_1O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OR_2$). Poisoning with these compounds may clinically resemble toxic alcohol poisoning. Glycol ethers commonly encountered include ethylene glycol butyl ether (also known as 2-butoxyethanol, ethylene glycol monobutyl ether, or butyl cellusolve), ethylene glycol methyl ether (2-methoxyethanol), and diethylene glycol (2,2′-dihydroxydiethyl ether). These compounds have many industrial uses, and are found in household and automotive products, such as hydraulic fluids, brake fluid, dry-erase board cleaner, paints, lacquers, and fog machine liquid. Use of the E-series glycol ethers (derivatives of ethylene glycol) has dramatically declined over the past few decades, as they have been replaced by the less-toxic P-series glycol ethers (derivatives of propylene glycol).[7,25] However, butoxyethanol is still in use because there are no P-series equivalents with the necessary physical properties.[25] Polyethylene glycol (PEG), as the name suggests, is a polymer of ethylene glycol with the structure $H(OCH_2CH_2)_nOH$. High molecular weight PEG is a waxy solid that is soluble in water, but not absorbed by the gastrointestinal tract when ingested, making it medically useful as an osmotic laxative. Different chain lengths have different physical properties, making PEG useful as an emulsifier and texturizer in many medicinal and food products.

HISTORY AND EPIDEMIOLOGY

Methanol was a component of the embalming fluid used in ancient Egypt. Robert Boyle first isolated the molecule in 1661 by distillation of boxwood, calling it *spirit of box*. The molecular composition was determined in 1834 by Dumas and Peligot, who coined the term *methylene* from the Greek roots for "wood wine." Industrial production began in 1923, and today most methanol is used for the synthesis of other chemicals. Methanol-containing consumer products that are commonly encountered include model airplane fuel, windshield washer fluid, solid cooking fuel for camping and chafing dishes (eg, Sterno cans), photocopying fluid, perfumes, and gas line antifreeze ("dry gas"). Methanol is also used as a solvent by itself, or as an adulterant in "denatured" alcohol. Most reported cases of methanol poisoning in the United States involve ingestions of one of the above products by individuals, with more than 60% caused by ingestion of windshield washer fluid, according to one review.[23] However, there have been sporadic epidemics of mass methanol poisoning, most commonly caused by tainted fermented beverages.[8,70] These epidemics are a continuing problem in other parts of the world.[78,139]

Ethylene glycol was first synthesized in 1859 by Charles Wurtz, and first widely produced as an engine coolant during World War II, when its precursor, ethylene oxide, became readily available. Today, its primary use remains as an engine coolant (antifreeze used in car radiators, as opposed to antifreeze used in gas tanks, which generally contains methanol).

Isopropanol is primarily available as rubbing alcohol. Typical household preparations contain 70% isopropanol. It is also a solvent used in many household, cosmetic, and topical pharmaceutical products. Perhaps because it is so ubiquitous, inexpensive, and its common name contains the word alcohol, isopropanol ingestions are the most common toxic alcohol exposure reported to poison centers in the United States,[132] typically as an ethanol substitute.

Most glycol ether poisoning is in the industrial setting because these products are so useful as solvents. Glycol ethers were also responsible for many poisoning epidemics in the 20th century. Diethylene glycol, when substituted for the more benign medication diluent propylene glycol, has repeatedly resulted in epidemics of acute renal failure largely in children from ingestion of contaminated elixirs. The first such epidemic involved an elixir of sulfanilamide in the United States, while subsequent epidemics in India, Nigeria, Bangladesh, and Haiti, have generally involved contaminated acetaminophen (Chap. 2).[38,85,103,118,133]

TOXICOKINETICS AND TOXICODYNAMICS

Alcohols are readily absorbed after ingestion,[36,42] but are not completely bioavailable, because of metabolism by gastric alcohol dehydrogenase, and because of first-pass metabolism by the liver. Although methanol also may be absorbed in significant amounts by inhalation, poisoning by this route is uncommon. In workers exposed to methanol fumes from industrial processes for up to 6 hours, in concentrations of 200 ppm (the Occupational Safety and Health Administration [OSHA] permissible exposure limit) there was no significant accumulation of methanol or formate.[77] However, cases of inhalational poisoning have been reported with intentional inhalation of methanol as a drug of abuse ("huffing") and with massive exposures of rescue workers responding to the scene of an overturned rail car filled with methanol.[3,37,83,128] Ethylene glycol and the glycol ethers have low volatility and are not reported to cause poisoning by inhalation. Most alcohols have some dermal absorption, although isopropanol, methanol, and the glycol ethers are able to penetrate the skin much better than can ethylene glycol.[27,79,129] Most reported cases of toxic alcohol poisoning by this route involve infants[22] (probably because of the greater surface-area-to-volume ratio in these patients), and likely also involved simultaneous inhalation. Some glycol ethers have high percutaneous absorption, and it appears that absorption is enhanced in the presence of water.[66,76]

Once absorbed, alcohols are rapidly distributed to total body water (Table 103–1). In human volunteers given very small oral dose of methanol on an empty stomach, the measured volume of distribution (Vd) was 0.77 L/kg, with a distribution half-life of about 8 minutes.[42] Although peak concentrations occured soon after ingestion in this investigation, anecdotal experience suggests that peak concentrations may be delayed after more consequential ingestions.

Without intervention, toxic alcohols are eliminated primarily through successive metabolism by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), each of which catalyzes an oxidation reaction coupled to the reduction of NAD^+ (oxidized form of nicotinamide adenine dinucleotide) to NADH (reduced form of nicotinamide adenine dinucleotide) and H^+ (hydrogen ion). Methanol is metabolized to formaldehyde, then formic acid (Fig. 103–1). Ethylene glycol has two hydroxyl groups that are serially oxidized by ADH and ALDH, producing, in turn, glycoaldehyde, glycolic acid, glyoxylic acid, and finally oxalic acid (Fig. 103–2).

TABLE 103–1. Toxic Alcohols: Characteristics, Signs, and Symptoms of Toxicity

Substance	Formula	Half-life	Metabolites	High Anion Gap Acidosis	Ketosis	CNS Depression	Characteristic Findings	Commercial Sources
Benzyl alcohol	C_6H_6OH	?	Benzoic acid, hippuric acid	+	–	+	Neonatal "gasping syndrome"	Bacteriostatic preservatives
Ethanol[a]	CH_3CH_2OH	Zero-order kinetics 15–20 mg/dL/h	Acetaldehyde, acetic acid	+	+	+	Intoxication	Solvents, beverages, colognes
Ethylene glycol	CH_2OHCH_2OH	8.5 h	Oxalic acid, glycolic acid	++	–	+	Renal failure, hypocalcemia, calcium oxalate crystals in urine	Antifreeze (95%), solvents, deicers, airconditioning units
Glycol ethers	$HOCH_2CH_2OR$	Varies	Varies	+	–	+	Similar to ethylene glycol	Solvents, industrial coatings
Isopropanol	$CH_3CHOHCH_3$	2.5–3.5 h	Acetone	–	+	++	Hemorrhagic tracheobronchitis	Rubbing alcohol, solvents, lacquer
Methanol	CH_3OH	Zero-order kinetics 8.5 mg/dL/h	Formaldehyde, formic acid	++	–	+	Blindness, pale edematous optic disc	Antifreeze, solvents, gasohol denaturant
Propylene glycol	$CH_2OHCHOHCH_3$	2–5 h	Lactic acid, pyruvic acid	+	–	+	Lactic acidosis	Solvents, deicers

+ = Presence and degree of symptoms; – = absence of symptoms.
[a]Only in the case of alcoholic ketoacidosis is there a high anion gap metabolic acidosis with ketonemia.

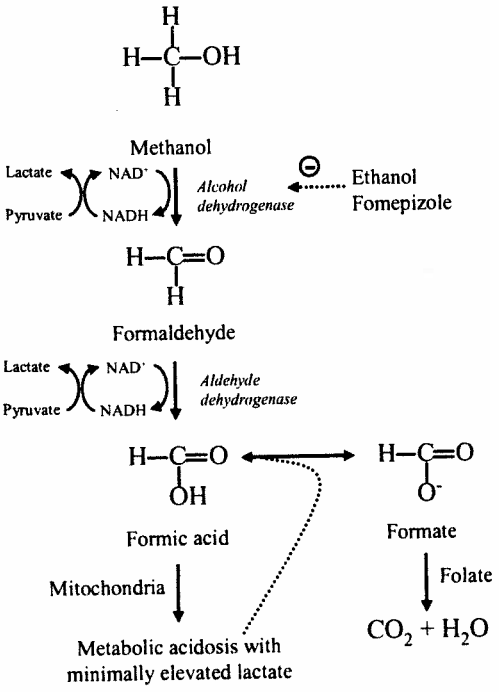


Figure 103–1. Major pathways of methanol metabolism. Metabolic acidosis worsens toxicity by shifting the equilibrium to favor the more toxic formic acid.

This metabolism, like ethanol metabolism by the same enzymes, is zero-order, with a rate that is reported to be about 10 mg/dL/h.[21,61,90] This rate is apparently unchanged in chronic ethanol users.[48,49]

Alternate minor metabolic pathways, such as catalase, exist for methanol and ethylene glycol. After methanol ingestion, the formate metabolite is bound by tetrahydrofolate and then undergoes metabolism by 10-formyltetrahydrofolate dehydrogenase to carbon dioxide and water. Ethylene glycol is metabolized to ketoadipate and glycine using thiamine and pyridoxine as cofactors. Because of the low toxicity of these metabolites, these normally minor metabolic pathways are attractive targets for potential therapy.

Methanol and ethylene glycol may also be eliminated from the body as unchanged parent compounds. When renal function is normal, ethylene glycol is slowly cleared by the kidneys, with a half-life of approximately 8.5 hours.[11,19,123] Methanol does not have significant renal elimination, and is cleared much more slowly than is ethylene glycol as a vapor in expired air (half-life 30–54 hours).[13,106]

CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

Central Nervous System Effects

All alcohols may cause inebriation, depending on the dose (Table 103–2). Based on animal data, it appears that higher-molecular-weight alcohols are more intoxicating than lower-molecular-weight

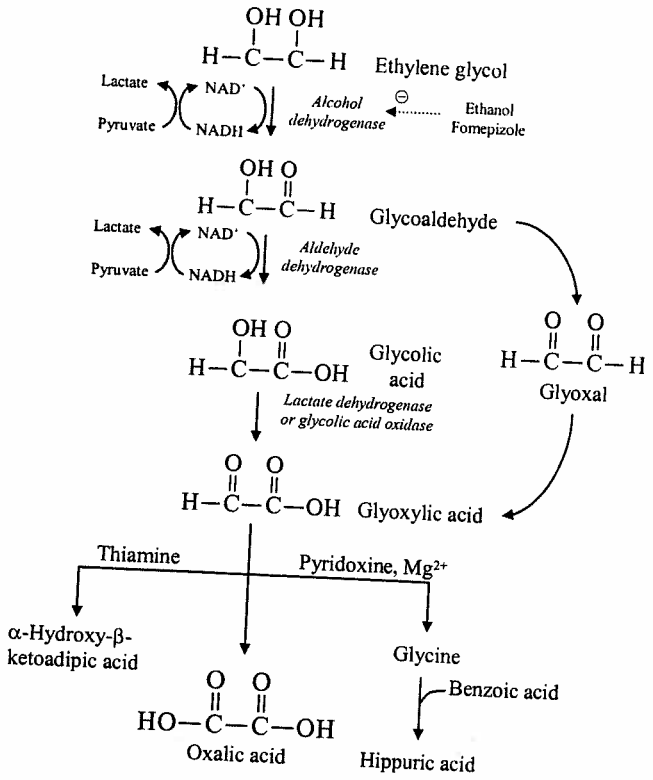


Figure 103–2. Pathways of ethylene glycol metabolism. Thiamine and pyridoxine enhance formation of nontoxic metabolites.

alcohols (eg, isopropanol ≈ ethylene glycol > ethanol > methanol).[13] However, the absence of apparent inebriation does not exclude toxic alcohol ingestion, particularly if the patient chronically drinks substantial quantities of ethanol and is tolerant of its CNS effects. This is intuitively obvious; serum methanol concentrations of 25–50 mg/dL are potentially associated with toxicity, although in most states individuals may legally drive a car with a serum ethanol concentration of up to 93 mg/dL (equivalent to a whole-blood concentration of 80 mg/dL as measured by breathalyzer).

The CNS manifestations of toxic alcohol poisoning are incompletely understood. It is assumed by analogy that toxic alcohol inebriation is similar to ethanol inebriation, in which case effects are mediated through increased GABAergic tone (both directly and through inhibition of presynaptic γ-aminobutyric acid type B [$GABA_B$] receptors) and inhibition of the *N*-methyl-D-aspartate (NMDA) glutamate receptors.[2,17,44,55,92] Although the CNS effects of other alcohols are clinically similar, there is no direct evidence that they are mechanistically the same.

Metabolic Acidosis

Metabolic acidosis with an elevated anion gap is a hallmark of toxic alcohol poisoning. This is a consequence of the metabolism of these alcohols to toxic organic acids. The acids have no rapid natural metabolic pathway of elimination (unlike acetic acid from ethanol metabolism, which can enter the Krebs cycle), and hence they accumulate. In methanol poisoning, formate is responsible for the acidosis (lactate may also contribute), whereas in ethylene glycol poisoning, glycolic acid is the primary acid responsible for the acidosis, with other metabolites making a minor contribution. Among the toxic alcohols,

TABLE 103–2. Signs and Symptoms of Toxic Alcohol Exposures

Organ System	Ethylene Glycol	Isopropanol	Methanol
Cardiovascular	Tachycardia Hypertension/hypotension Dysrhythmias Myocarditis	Tachycardia Hypotension Myocardial depression	Tachycardia Hypotension
Central nervous	Ataxia Meningoencephalitis Convulsions CNS depression Intoxication Myoclonus Cranial nerve abnormalities	Areflexia Ataxia CNS depression Dizziness Headache Intoxication Muscle weakness Hypothermia	CNS depression Convulsions Dizziness Headache Hypothermia Intoxication
Gastrointestinal	Nausea, vomiting	Abdominal pain, cramping Gastritis Hematemesis Nausea, vomiting	Abdominal pain Anorexia Gastritis Nausea, vomiting Pancreatitis
Ophthalmic	Ophthalmoplegia Nystagmus		"Snow fields" Blurred vision Hyperemic optic discs Mydriasis Papilledema, blindness
Pulmonary	Hyperventilation, tachypnea, pneumonitis Respiratory depression	Odor of acetone Respiratory depression	Respiratory depression
Renal	Crystalluria Renal insufficiency	Hemorrhagic tracheobronchitis Renal tubular acidosis	
Other		Rhabdomyolysis Hemolytic anemia	

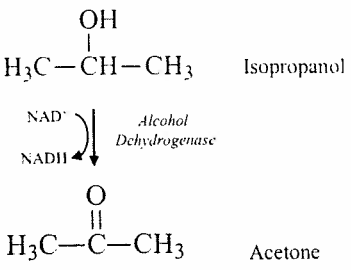


Figure 103–3. Isopropanol metabolism.

isopropanol is unique in that it is not metabolized to an acid metabolite but instead is metabolized to acetone. Acetone is a ketone, not an aldehyde, and therefore cannot be further metabolized by ALDH (Fig. 103–3). Thus isopropanol has no organic acid metabolite and does not cause metabolic acidosis. In fact, ketosis without acidosis is the defining characteristic of isopropanol poisoning.

Specific End-Organ Effects

Additional end-organ effects depend on which alcohol is involved. Methanol causes visual impairment ranging from blurry or hazy vision or defects in color vision, to "snowfield vision" or total blindness in severe poisoning. On physical examination, central scotoma may be present on visual field testing, and both hyperemia and pallor of the optic disc, and papilledema are described as characteristic findings.[8,104,142] The formate metabolite of methanol is a mitochondrial toxin, inhibiting cytochrome oxidase (much like cyanide) and thereby interfering with oxidative phosphorylation.[31,98,99] Although it is unclear why this results in ocular toxicity while other tissues are relatively spared, retinal pigmented epithelial cells and optic nerve cells appear to be uniquely susceptible.[29,86,126,127]

Interestingly, neurons in the basal ganglia appear to be similarly susceptible to this toxicity; bilateral basal ganglia lesions (particularly putamen and, less commonly, caudate nucleus) characteristically are visualized on cerebral computerized tomography or magnetic resonance imaging after methanol poisoning.[26,34,50,51,107] Although lesions of this type are nonspecific and can occur in other disease states (eg, hypoxia, hypotension, and carbon monoxide exposure), they may occur in the absence of hypotension and hypoxia in methanol poisoning,[88] suggesting a direct toxic mechanism. Rarely, injury to other tissues may also occur; both renal failure and pancreatitis are reported after methanol poisoning.[52,73] For unclear reasons, one case series showed a very high incidence of pancreatitis (50%).[52] Myoglobinuria and resultant acute renal failure have also occurred in a case of severe methanol poisoning.[46]

The most prominent end-organ effect of ethylene glycol is nephrotoxicity. The oxalic acid metabolite forms a complex with calcium to precipitate as crystals in the renal tubules, leading to acute renal failure.[35,89] In addition, the intermediate products of ethylene glycol metabolism are directly toxic to the renal tubules by a mechanism yet to be described, causing acute tubular necrosis and thereby contributing to renal failure.[20,35,110,112] Furthermore, although oxalic acid has long been recognized as a toxicant to renal tubules, it generally does not cause glomerular injury;[67] thus the presence of necrotic lesions to the glomerular basement membrane on some pathology specimens provides indirect evidence that oxalic acid is not solely responsible for the nephrotoxicity of ethylene glycol.[35]

Ethylene glycol can occasionally affect other organ systems. In severe poisoning, the oxalic acid metabolite may be present in sufficient amounts to cause hypocalcemia by precipitation with calcium. This can result in prolongation of the QTc interval on the electrocardiogram and dysrhythmias.[120] Precipitation of calcium oxalate crystals in the brain has also been found on autopsy after severe ethylene glycol poisoning.[1,35] This may account for the multiple cranial nerve abnormalities that occasionally develop,[124] although there is as yet no evidence of causation. A leukemoid reaction may also occur in the setting of severe ethylene glycol poisoning, although the mechanism remains unclear.[96]

Hemorrhagic gastritis has been reported in association with isopropyl alcohol intoxication. Although this has been assumed to be caused by a local irritant effect, one reported case of hemorrhagic gastritis after percutaneous isopropanol exposure suggests that this is not the only mechanism, and, in fact, may be a specific end-organ effect.[29]

DIAGNOSTIC TESTING

Toxic Alcohol Concentrations

Actual serum methanol, ethylene glycol, and isopropanol concentrations are in theory the ideal tests to perform when toxic alcohol poisoning is suspected shortly after exposure. However, these concentrations are most commonly measured by gas chromatography with or without mass-spectrometry confirmation, methodologies that are not available in most hospital laboratories on a 24-hour basis, if available at all. In fact, in many hospitals, these are only available as "send-out" tests, so results arrive too late for early clinical decision making.[71] Enzymatic assays for methanol, formic acid, ethylene glycol, and glycolic acid have been developed,[9,125,130] and these may lead to more readily available clinical tests, but a commercial product is currently approved for veterinary use only. A group in Finland described a point-of-care breath test for methanol, using a portable Fourier transform infrared (FT-IR) analyzer similar to the "breathalyzers" used by law enforcement agents.[75] Although analyzers like this are used to check for methanol as a combustion product in industry, they are not yet approved for medical use in the United States. Once approved, they would be ideal for early clinical decision analysis because they are easy to use and provide a rapid result. They also can provide continuous monitoring of concentrations, a feature that would be very helpful during hemodialysis. Unfortunately, this methodology cannot be used to detect ethylene glycol because of its low volatility.

Patients presenting late after ingestion may already have metabolized all parent compound to toxic metabolites, and thus may have low or no measurable toxic alcohol concentrations. An enzymatic assay for glycolic acid may be more helpful in late cases of ethylene glycol ingestion. Some authors have actually advocated routine testing for glycolic acid in addition to testing for the parent compound when ethylene glycol poisoning is suspected.[112] Similarly, a formic acid concentration may be valuable when a patient presents late after methanol ingestion.[105] Clearly, a low or undetectable toxic alcohol concentration must be interpreted within the context of the history and other clinical data, such as the presence of acidosis and end-organ toxicity, with glycolic acid and formic acid concentrations as potentially valuable additions.

Samples must be handled correctly for accurate toxic alcohol results. Particularly with the more volatile alcohols methanol and isopropanol, concentrations may be falsely low if the sample tubes

are not airtight. This loss of volatile alcohol commonly results in low concentrations if alcohol concentrations are done as "add-on" tests to samples already opened for electrolyte or osmol determinations.

Other alcohols, such as benzyl alcohol and propylene glycol, as well as the glycol ethers, are not routinely assessed by gas chromatography. Thus, these xenobiotics present a much greater diagnostic challenge than methanol and ethylene glycol. Enzymatic assays for methanol or ethylene glycol would also fail to detect benzyl alcohol and propylene glycol, although false-positive ethylene glycol tests may occur if propylene glycol is present. Consequently, a high index of suspicion is critical to making the diagnosis in these cases. If suspected on the basis of history, specific toxic alcohol testing should be performed.

Once alcohol concentrations are obtained, their interpretation represents a further point of controversy. Traditionally, a methanol or ethylene glycol level greater than 25 mg/dL has been considered toxic, but the evidence supporting this as a threshold is often questioned. In a case series of methanol-poisoned patients from the 1950s, a methanol level of 52 mg/dL was the lowest associated with vision loss.[8] This may have been the origin of the 25 mg/dL threshold, incorporating a 50% reduction as a margin of safety. However, the patient with the 52-mg/dL concentration presented 24 hours after his initial ingestion, and therefore was much more severely poisoned than suggested by his serum concentration at that point. In fact, almost all reported cases of methanol poisoning involve late presenters with metabolic acidosis.[74] The only reported patient who went untreated after presenting early with only an elevated methanol concentration (45.6 mg/dL) and no acidosis never developed acidosis or end-organ toxicity.[12,74] However, until better data is available, most experts continue to use 25 mg/dL as a threshold for treatment.

Because of the problems with obtaining and interpreting actual serum concentrations, many surrogate markers have been used to assess the patient with suspected toxic alcohol poisoning. The initial laboratory evaluation should include serum electrolytes (including calcium), blood urea nitrogen, serum creatinine, urinalysis, measured serum osmolality, and a serum ethanol concentration. An arterial blood gas analysis with a lactate concentration is also helpful in the initial evaluation of ill-appearing patients.

Anion Gap and Osmol Gap

For a full discussion of the anion gap concept, see Chap. 17. As discussed above, anion gap elevation is a hallmark of toxic alcohol poisoning. In fact, the possibility of methanol or ethylene glycol poisoning is often first considered when patients present with an anion gap acidosis of unknown etiology, frequently with no history of an ingestion. Unless other clinical information suggests otherwise, it is important to exclude lactate-associated acidosis and ketoacidosis in these patients (the most common causes of anion gap acidosis), before pursuing toxic alcohols. This is because of the extensive evaluation and expensive, potentially invasive course of therapy to which the individual would be committed. However, elevated lactate concentrations may be present in the setting of both methanol and ethylene glycol poisoning.

The unmeasured anions in toxic alcohol poisoning are the dissociated organic acid metabolites discussed above. The acidosis takes time to develop, sometimes as long as 24 hours for methanol. Thus, the absence of an anion gap elevation early after reported toxic alcohol ingestion does not exclude the diagnosis. If ethanol is present in the body, the development of acidosis will not begin to occur until the ratio of the ethanol to the toxic alcohol falls below a number that varies by alcohol.

A potential early surrogate marker of toxic alcohol poisoning is an elevated *osmol gap* (discussed in detail in Chap. 17). However, it is important to recognize that osmol gap elevation is neither sensitive nor specific for toxic alcohol poisoning. Because a baseline osmol gap is generally not available when evaluating a patient, and a normal osmol gap ranges from −14 to +10, so-called normal osmol gaps cannot exclude toxic alcohol poisoning.[58] For example, in a patient with a baseline osmol gap of −10, a gap of +5 represents a methanol concentration of 47 mg/dL, or an ethylene glycol concentration of 93 mg/dL, concentrations that might require hemodialysis. Inversely, a moderately elevated osmol gap (+10 to +20) is not necessarily diagnostic of toxic alcohol poisoning because many other disorders, such as alcoholic ketoacidosis and lactate-associated acidosis, may raise the osmol gap.[119] However, a markedly elevated osmol gap (>50) is difficult to explain by anything other than a toxic alcohol.

Further complicating matters, the anion gap and osmol gap have a reciprocal relationship over time. This is because soon after ingestion, the alcohols present in the serum raise the osmol gap, but do not affect the anion gap, because metabolism to the organic acid anion has not yet occurred. As the alcohols are metabolized to organic acid anions, the anion gap, rises while the osmol gap falls, because the metabolites are negatively charged particles that have already been accounted for in the calculated osmolarity by doubling of the sodium. Thus in theory patients who present early after ingestion may have a high osmol gap and normal anion gap, whereas those who present later may have the reverse.[59,60] Figure 103–4 depicts a more intuitive visual representation of this process.

Ethanol Concentration

A serum ethanol concentration is an important part of the assessment of the patient with suspected toxic alcohol poisoning. As discussed in Chap. 17, the ethanol concentration is necessary for the calculation of osmolarity. In addition, because ethanol is the

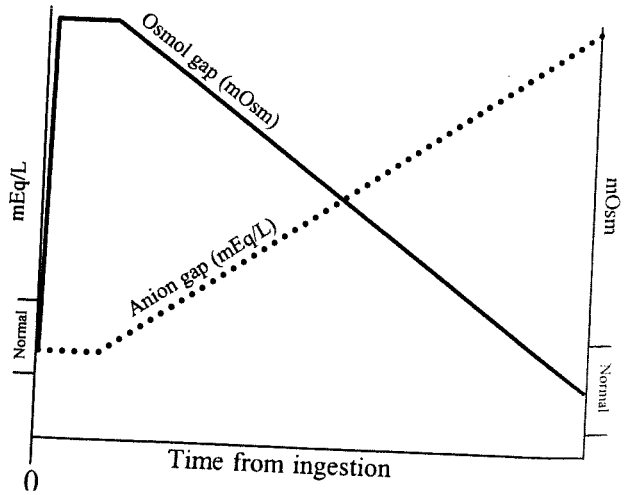


Figure 103–4. The reciprocal relationship of anion gap and osmol gap over time. Note that patients presenting shortly after an ingestion may have a normal anion gap, whereas patients who present at a later time may have a normal osmol gap.

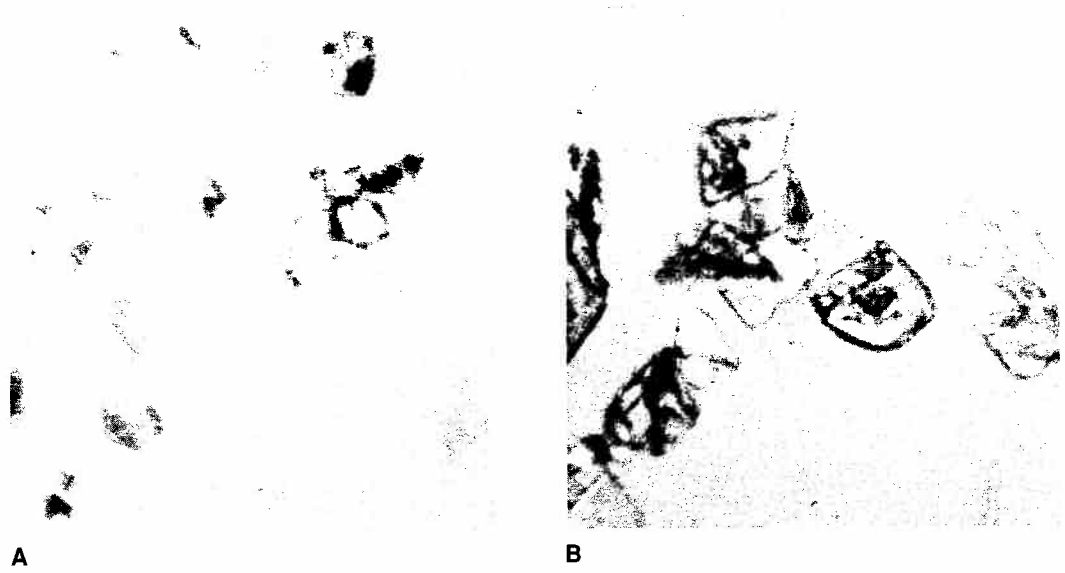


Figure 103–5. Calcium oxalate crystals (dehydrate forms) under low **(A)** and high **(B)** power, found in the urine of a patient following the ingestion of ethylene glycol.

preferred substrate of alcohol dehydrogenase (4:1 over methanol, and 8:1 over ethylene glycol), a significant concentration would be protective if coingested with a toxic alcohol. In fact, ethanol concentrations near 100 mg/dL virtually preclude toxic alcohols as the cause of an unknown anion gap metabolic acidosis because the presence of such a concentration should have prevented metabolism to the organic acid, except when ethanol is ingested several hours after significant amounts of a toxic alcohol.[56]

Lactate

Both methanol and ethylene glycol can result in elevated lactate concentrations, for very different reasons. Formate, as an inhibitor of oxidative phosphorylation, can lead to anaerobic metabolism and resultant lactate elevation. Additionally, metabolism of all alcohols results in an increased NADH-to-NAD^+ ratio, which favors the production of lactate from pyruvate. Furthermore, hypotension and organ failure in severely poisoned patients can also result in elevated lactate concentrations. Lactate production by these mechanisms tends to result in serum concentrations less than 5 mmol/L.

In ethylene glycol poisoning, the glycolate metabolite may also cause a false-positive lactate elevation when measured by some analyzers, particularly those that analyze whole-blood arterial blood gases. Specific models implicated include ABL 625, Beckman LX 20, Chiron 865, Bayer (formerly Chiron) 860, and to a lesser extent, Hitachi 911 analyzers, but not the Vitros 950.[93,111,138] The artifact results from the lack of specificity of the lactate oxidase enzyme used in these machines,[93,111,138] although direct oxidation of glycolate at the analyzer anode has also been suggested as a possible mechanism.[121] The presence of a "lactate gap" might also be used to diagnose ethylene glycol poisoning in hospitals where multiple lactate assays are available that are with and without sensitivity to glycolate.[121]

Other Diagnostics

The urine may provide information in the assessment of the patient with suspected ethylene glycol poisoning. Calcium oxalate monohydrate (spindle-shaped) and dihydrate (envelope-shaped) crystals may be seen when the urine sediment is examined by microscopy, although this finding is neither sensitive nor specific (Fig. 103–5).[61] In one series, calcium oxalate crystals were present in the urine of only 63% (12 of 19) of patients with proven ethylene glycol ingestion.[14]

Some brands of antifreeze contain fluorescein to facilitate the detection of radiator leaks. If one of these products is ingested and the urine is examined with a Woods lamp within the first 6 hours, there may be urinary fluorescence.[137] False-positive fluorescence may result from examining the urine in glass or plastic containers because of the inherent fluorescence of these materials, so if this test is performed, an aliquot of the urine should be poured onto a piece of white gauze or paper. Recent work suggests that this test is not useful; almost all children had urinary fluorescence in one study.[18]

The evaluation of patients with known or suspected ethylene glycol poisoning should also include a serum calcium concentration and a creatinine concentration. Patients with methanol poisoning and abdominal pain also warrant an assessment of liver enzymes and serum lipase and/or amylase concentrations, because of the possibility of associated hepatitis and pancreatitis.

MANAGEMENT

As always, immediate resuscitation of critically ill patients starts with management of the airway, breathing, and circulation. Because alcohols may cause respiratory depression and coma, intubation and mechanical ventilation are commonly necessary for patients with severe poisoning. Alcohol-induced vasodilation, combined with vomiting, often lead to hypotension, and many patients will require fluid resuscitation with intravenous crystalloid. Gastrointestinal decontamination is rarely, if ever, indicated for toxic alcohols, because of their rapid absorption and limited binding to activated charcoal. However, placement of a nasogastric tube and aspiration of any gastric contents is probably worthwhile

in intubated patients, as absorption may sometimes be delayed after a large dose.[31]

Alcohol Dehydrogenase Inhibition

The most important part of the initial management of patients with known or suspected toxic alcohol poisoning (after initial resuscitation) is blockade of ADH. This allows for the establishment of a definitive diagnosis and arrangement for hemodialysis while preventing the formation of toxic metabolites. Additionally, in some cases ADH blockade may itself serve as definitive therapy.

Teleologically, ADH exists for the purpose of metabolizing ethanol, so it is not surprising that the enzyme has a higher affinity for ethanol than for other alcohols. In fact ADH has an affinity for ethanol that is 15 times greater in vitro than its affinity for methanol, and 67 times greater than its affinity for ethylene glycol on a molar basis.[108,109] Thus significant concentrations of ethanol prevent metabolism of other alcohols to their toxic products. Ethanol is the traditional method of ADH inhibition and still the only option in some institutions. A 10% solution is administered through a central venous catheter and titrated to maintain a serum concentration of 100 mg/dL (see Antidotes in Depth: Ethanol). Complications of the infusion, although uncommon,[117] include hypotension, respiratory depression (with supratherapeutic concentrations), flushing, hypoglycemia, hyponatremia, pancreatitis, and gastritis, as well as inebriation, so patients getting intravenous ethanol require admission to an intensive care unit. Orally administered ethanol is also effective, and may be considered when intensive monitoring is unavailable, particularly in rural areas where there may be a significant delay in getting the patient to a hospital.

Fomepizole is a more recently developed competitive antagonist of ADH that has many advantages over ethanol. It reliably inhibits ADH when administered as an intravenous bolus every 12 hours, and concentrations do not need to be monitored as with an ethanol infusion.[13,14] It does not cause inebriation and is associated with few adverse effects, so it does not require intensive care unit monitoring.[4,5,13,14] For these reasons, it has become the preferred method of ADH blockade, despite being significantly more expensive than ethanol. In fact, the savings in intensive care unit (ICU) monitoring and laboratory costs probably compensate for the higher drug cost of fomepizole, unless the patient requires intensive monitoring anyway based on the severity of illness.[11] The dose of fomepizole is 15 mg/kg intravenously as an initial loading dose followed by 10 mg/kg every 12 hours. After 48 hours of therapy, fomepizole induces its own metabolism, so the dose must be increased to 15 mg/kg every 12 hours.

Indications for ethanol or fomepizole therapy may be based on the history or on laboratory data. Any patient with a believable history of methanol or ethylene glycol ingestion should be treated until concentrations are available because, as discussed above, early symptoms and laboratory markers (other than serum concentrations) may be absent. In addition, any patient with an anion gap acidosis without another explanation or a markedly elevated osmol gap should also be treated. Once concentrations are available, therapy should be continued until the serum concentration is below 25 mg/dL, although as discussed above, this number is based more on consensus opinion than on data.

Hemodialysis

The definitive therapy for patients poisoned by toxic alcohols is hemodialysis. Hemodialysis clears both the alcohols and their toxic metabolites from the blood, and can correct the acid–base status disorder. The indications for hemodialysis have become more controversial with the advent of fomepizole because of its effectiveness combined with its low incidence of adverse effects. Ethylene glycol can generally be expected to be cleared within a few days once ADH is blocked and the glomerular filtration rate (GFR) is normal, and some clinicians argue that the risks of an invasive procedure like hemodialysis are not warranted, except for astronomical concentrations. However, patients with end-organ toxicity or severe acidosis have significant amounts of toxic metabolites, a problem not addressed by ADH blockade, and acidosis is associated with poor prognosis.[82] In addition, patients with renal failure will not eliminate the parent compound once ADH is blocked, except very slowly in expired air, in the case of methanol. Therefore, there is a consensus that metabolic acidosis, signs of end-organ toxicity (including coma and seizures), and renal failure are indications for hemodialysis. A "toxic level," and possibly a very high osmol gap are more relative indications for hemodialysis, and decisions must be based on the judgement of the physician for the specific clinical scenario, taking into account the available resources. Some authors have advocated using toxic metabolite concentrations (if available) as additional criteria for hemodialysis. In data from case series, an elevated formate concentration appears to be a better predictor than methanol concentrations of clinically important toxicity.[105] Similarly, glycolic acid concentrations are a better predictor than ethylene glycol concentrations of death and renal failure.[112] However, although clearance of formate by hemodialysis is substantial,[64,65,72] the overall clearance in one case series did not appear to increase significantly above endogenous concentrations in patients also treated with folate and bicarbonate.[72] Some have questioned the data quality in this series.[140]

The American Academy of Clinical Toxicology (AACT) practice guidelines are ambiguous with respect to a threshold methanol concentration for hemodialysis in the absence of acidosis, renal failure, end-organ effects, or worsening clinical status.[4] The AACT guidelines for ethylene glycol actually advise against hemodialysis for a concentration alone, without any of these clinical indications.[5] Clearly, there is still insufficient data to establish threshold concentrations of alcohols or their metabolites where dialysis is absolutely indicated, and the decision is ultimately a subjective one based on the overall clinical scenario.[57] However, until more work is done, a methanol concentration of 25 mg/dL remains a reasonable indication for hemodialysis. An ethylene glycol concentration of 50 mg/dL in the absence of alcohol dehydrogenase blockade or abnormal renal function also should be consider a reasonable indication.

Although hemodialysis effectively clears isopropanol and acetone from the blood, it is rarely, if ever, indicated for this purpose. Because isopropanol does not cause a metabolic acidosis and very rarely results in significant end-organ effects, the risks of hemodialysis likely outweigh the benefits.

Many patients will require multiple courses of hemodialysis to clear the toxic alcohol. A formula may enable the nephrologists to estimate the dialysis time required.[54] Pharmacokinetically hemodialysis is a first order process and will decrease the toxic alcohol concentration by half in about 2½ hours (HD clearance, 225 mL/min). ADH blockade should be continued during and after hemodialysis until a subsequent concentration of the offending xenobiotic is confirmed to be nontoxic. Ethanol infusion rates must be increased during hemodialysis to maintain a therapeutic serum concentration as the ethanol is cleared (see Antidotes in Depth: Ethanol). Fomepizole should be redosed every 4 hours during hemodialysis to maintain therapeutic serum levels.[4,5]

Adjunctive Therapy

There are several therapeutic adjuncts to ADH blockade with or (especially) without hemodialysis that should be considered for these patients. One difference that has been invoked to explain the absence of retinal toxicity from methanol in some species is the relative abundance of hepatic folate stores in these species (such as the rat). Folate and leucovorin enhance the clearance of formate in animal models.[101,102] Thiamine enhances the metabolism of ethylene glycol to ketoadipate, and pyridoxine enhances its metabolism to glycine (and, ultimately, to hippuric acid). Although all of these modalities offer theoretical advantages, they have yet to be proven to change outcome in humans. However, there is one human case report showing enhanced formate elimination with folinic acid therapy.[63] Additionally, some authors have suggested that an apparent lack of an increase in formate clearance by hemodialysis was because it was dwarfed by the effectiveness of folate supplementation in both the study group and the control group.[72] Because of the safety of vitamin supplementation, the potential benefit likely outweighs the risk of therapy (see Antidotes in Depth: Thiamine Hydrochloride and Antidotes in Depth: Folic Acid and Leucovorin [Folinic Acid]).

Formate (dissociated formic acid), is much less toxic than the undissociated formic acid, likely because undissociated formic acid has a much higher affinity for cytochrome oxidase in the mitochondria, the ultimate target site for toxicity.[81] In addition, the undissociated form is better able to diffuse into target tissues.[65] Alkalinization with a bicarbonate infusion shifts the equilibrium to favor the less toxic, dissociated form, in accordance with the Henderson-Hasselbalch equation. This also enhances formate clearance in the urine by ion trapping.[65] Uncontrolled case series data have shown that patients treated with bicarbonate alone had better than expected outcomes after severe methanol poisoning,[97] but the results are equivocal in patients also treated with ADH blockade and hemodialysis.[13,62,91] Additionally, the severity of the metabolic acidosis after methanol poisoning is a good predictor of severe neurologic effects such as coma and seizures,[82] although alkalinization has not been proven to prevent these effects. However, in the absence of contraindications to a bicarbonate infusion (eg, hypokalemia, volume overload), alkalinization should be used in the patient with suspected methanol poisoning and a significant acidosis. A blood pH greater than 7.20 is a reasonable end point. Alkalinization should also be considered for patients with ethylene glycol poisoning and significant metabolic acidosis.

OTHER ALCOHOLS

Propylene Glycol

Propylene glycol is commonly used as an alternative to ethylene glycol in "environmentally safe" antifreeze. It is also used as a diluent for many pharmaceuticals (such as phenytoin and lorazepam). When this alcohol is successively metabolized by ADH and ALDH to lactate, lactic acidosis results. (Fig. 103–6). This metabolism can result in extremely high lactic acid levels—levels that would be incompatible with life, if generated by any other disease process. In other disease states associated with lactate accumulation and acidosis, the lactate is a reflection of underlying anaerobic metabolism, a marker of severe illness rather than part of the underlying pathophysiology. Lactic acidosis from propylene glycol is surprisingly well tolerated because it represents nothing more sinister than itself, and it is rapidly cleared by oxidation to pyruvate, which then undergoes normal carbohydrate metabolism. (Chapter 53 further discusses propylene glycol.)

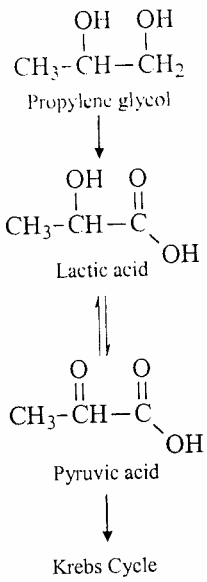
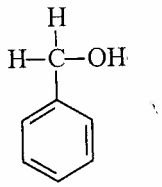


Figure 103–6. Propylene glycol metabolism to lactic acid. Under normal conditions, lactate is converted to pyruvate which, following decarboxylation, enters the Krebs cycle.

Benzyl Alcohol



Benzyl alcohol used as a preservative for intravenous solutions. It is no longer used in neonatal medicine, because it was responsible for "neonatal gasping syndrome," involving multiorgan system dysfunction, metabolic acidosis, and death from its metabolism to benzoic acid and hippuric acid.[39,84] (Chapter 53 further discusses benzyl alcohol.)

GLYCOL ETHERS

Diethylene Glycol

Diethylene glycol's toxicity in humans was first recognized in 1937 after the elixir of sulfanilamide disaster. Clinical manifestations typically begin with abdominal pain, nausea, and vomiting, followed by worsening metabolic acidosis, acute renal failure, and progressive mental status depression over several days.[53,115] Epidemic poisoning in children is also manifested by liver failure, respiratory failure, and neurotoxicity, including seizures, optic neuritis, and paresthesias.[10,103,122] Two cases of adults with

intentional diethylene glycol ingestions resulted in peripheral neuropathy,[53,115] and two other adults had peripheral demyelination and axonal degeneration at autopsy.[28] Despite this pathologic evidence of demyelination, the only reported patient to have nerve conduction studies performed after diethylene glycol ingestion, suggested evidence of an axonopathy.[53] The patient developed total quadriplegia, then recovered motor function over the course of several months.[53]

It is unclear whether toxicity is caused by the diethylene glycol parent compound or a metabolite. It appears that the ether linkage is stable in the body; ethylene glycol was not detectable in one patient with severe diethylene glycol poisoning,[53] nor could it be detected in a rat model of diethylene glycol poisoning, in which 2-hydroxyethoxyacetic acid was an identified metabolite.[136] It is also unclear whether this metabolism to 2-hydroxyethoxyacetic acid occurs in humans, or whether this metabolism occurs through alcohol dehydrogenase and aldehyde dehydrogenase. In rats, fomepizole blocks this metabolism.[136] However, although one child demonstrated minimal toxicity after diethylene glycol ingestion when treated with fomepizole and hemodialysis,[15] another patient suffered severe toxic effects despite early fomepizole therapy.[115]

Based on the limited currently available evidence, it is reasonable to initiate fomepizole therapy, as well as hemodialysis, in patients who present early after diethylene glycol ingestion. Patients who present late after ingestion are likely to need hemodialysis for renal failure.

Butoxyethanol

Most cases of butoxyethanol poisoning involve adults with intentional ingestions.[6,16,41,47,87,113] Unintentional exposures in children to household glass cleaners containing butoxyethanol typically result in few adverse effects.[25,132] Cases of butoxyethanol poisoning are likely to continue to occur, because it has very useful physical properties as an amphiphilic solvent with a low evaporation rate and high flash point, and a suitable replacement in industry has not yet been found.[72] The disposition of butoxyethanol after ingestion is still not entirely clear, but Figure 103–7 summarizes what is known. It does not appear that metabolism to ethylene glycol occurs in humans, but this remains controversial.

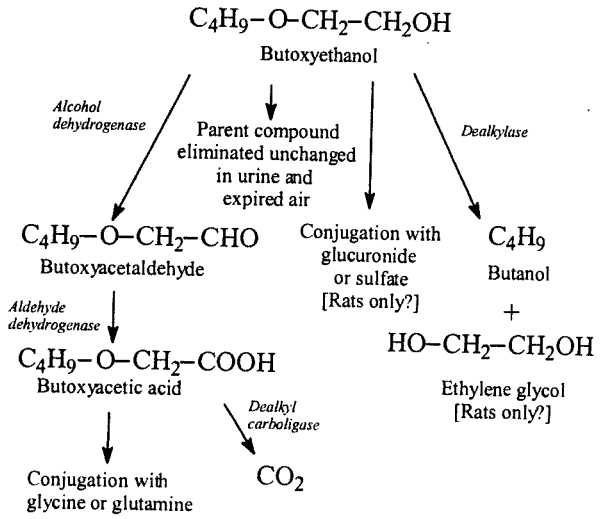


Figure 103–7. Elimination of butoxyethanol. It is still not certain whether dealkylation and ethylene glycol formation occur in humans.[39]

Clinical manifestations of acute butoxyethanol toxicity may include mental status depression, hypotension, hyperchloremic metabolic acidosis, acute renal failure, hemolysis, nonhemolytic anemia, hematuria, acute lung injury, and mild elevation of the aminotransferases.[6,16,41,47,87,113] Chronic occupational exposure may also cause adverse effects. Although butoxyethanol does not increase cancer rates in rats, it does lead to hemangiosarcomas in male mice and forestomach tumors in female mice.[33,43,95] The US Environmental Protection Agency has said that it could not yet determine whether butoxyethanol is a human carcinogen, and effects on fetal development are also unclear.[33,40,80,95]

Partly because its metabolism and mechanism of toxicity are incompletely understood, the optimal therapy for acute butoxyethanol poisoning is still controversial. Good outcomes have been reported after ethanol therapy alone,[87] and after ethanol and bicarbonate therapy with hemodialysis.[47] In another case, however, hemodialysis did not appear to hasten butoxyethanol elimination and persistent neurologic deficits resulted.[16] At present, alcohol dehydrogenase inhibition with ethanol or fomepizole is a reasonable intervention. Hemodialysis may be considered in patients with severe acidosis.

Ethylene Glycol Monomethyl Ether

Ethylene glycol monomethyl ether poisoning should be increasingly rare in the future, because recognition of its substantial toxicity has greatly limited its use. For example, in Sweden, its use diminished from 260 tons per year in 1993 to 19 tons per year in 1997.[68] In the United States, production has declined by more than 95% over the past 20 years.[135] After exposure, 86% of ethylene glycol monomethyl ether is metabolized to 2-methoxyacetic acid and excreted in the urine.[44,68] Ethanol and pyrazole completely block this metabolism in rat models, suggesting that this metabolism involves alcohol dehydrogenase.[94,116] Clinical manifestations after acute exposure are rare, with only 3 cases reported. One man developed hemorrhagic gastritis and liver, kidney, and pancreatic toxicity that ultimately proved fatal.[141] Two men recovered after developing confusion, nausea, and weakness, followed by metabolic acidosis, tachycardia, tachypnea, and renal failure in one case.[100] Based on current understanding of ethylene glycol monomethyl ether metabolism, acute toxicity should be treated with alcohol dehydrogenase blockade, although there are not yet human outcome data to support the practice.

Chronic hematologic effects, typically after inhalation or dermal exposure, include bone marrow suppression resulting in anemia, leucopenia, or pancytopenia in severe cases.[135] Reproductive effects include oligospermia or azoospermia in men[134] and increased frequency of spontaneous abortions in women.[135] Teratogenicity has also occurred in animal models of ethylene glycol monomethyl ether exposure, as well as in human populations with known exposure (eg, workers in the semiconductor industry).[135] Obviously, removal from exposure is the most important element of clinical management for these patients.

SUMMARY

Toxic alcohol poisoning is complex and may result in consequential toxicity. Early symptoms may include inebriation, and subsequent toxicity results from metabolism to organic acid anions that cause metabolic acidosis and end-organ effects. The time required

for this metabolism results in a delay before toxicity clinically manifests itself. Until serum concentrations are available, the serum anion gap and osmol gap may help with decision making but do not exclude toxicity if the history is concerning. Therapy consists of ADH antagonism with fomepizole or ethanol, as well as adjunctive therapy with bicarbonate, folate or folinic acid, pyridoxine, and thiamine. Hemodialysis is the definitive therapy because it removes the alcohol and the toxic metabolites while correcting the metabolic acidosis and electrolyte abnormalities. However, hemodialysis may have a more limited role in the future, particularly for ethylene glycol poisoning, because of the safety and efficacy of fomepizole.

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