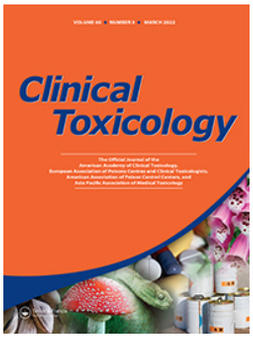

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American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning

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ARTICLE

American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning

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ABSTRACT

Fomepizole (4-methylpyrazole, 4-MP, Antizol™) is a potent inhibitor of alcohol dehydrogenase that was approved recently by the US Food and Drug Administration (FDA) for the treatment of ethylene glycol poisoning. Although ethanol is the traditional antidote for ethylene glycol poisoning, it has not been studied prospectively. Furthermore, the FDA has not approved the use of ethanol for this purpose. Case reports and a prospective case series indicate that the intravenous (IV) administration of fomepizole every 12 hours prevents renal damage and metabolic abnormalities associated with the conversion of ethylene glycol to toxic metabolites. Currently, there are insufficient data to define the relative role of fomepizole and ethanol in the treatment of ethylene glycol poisoning. Fomepizole has clear advantages over ethanol in terms of validated efficacy, predictable pharmacokinetics, ease of administration, and lack of adverse effects, whereas ethanol has clear advantages over fomepizole in terms of long-term clinical experience and acquisition cost. The overall comparative cost of medical treatment using each antidote requires further study.

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TREATMENT GUIDELINES

The determination of plasma ethylene glycol concentrations is the definitive method for the diagnosis of ethylene glycol poisoning. Frequently, this laboratory test is not available immediately and therefore the initiation of treatment with an antidote depends on the clinical presentation and other laboratory measurements in addition to the plasma ethylene glycol concentration. Table 1 lists the criteria for the use of antidotes during the treatment of ethylene glycol poisoning. After the diagnosis of documented or suspected ethylene glycol poisoning, Table 2 outlines the treatment plan.

Epidemiology

During the early 1900s, ethylene glycol was considered nontoxic. The first cases of ethylene glycol toxicity were reported in 1930 when two young men developed terminal respiratory failure and convulsions after ingesting Prestone® antifreeze (95% ethylene glycol).[1] The accessibility of ethylene glycol, its intoxicating properties, and its sweet taste resulted in the use of ethylene glycol as a substitute beverage for ethanol. Epidemics of ethylene glycol poisoning occurred during World War II[2] and during the 1973 Arab-Israeli conflict. Eighteen soldiers who ingested ethylene glycol as a substitute for ethanol died during World War II.[3] In October 1973, the ingestion of antifreeze-contaminated drinking water caused toxicity in at least 22 soldiers and 1 death.[4] Serious cases of ethylene glycol poisoning are more sporadic in the civilian population where intentional ingestions usually involve attempted suicide or the substitution of ethylene glycol for alcohol.[5]

As recently as the late 1950s, 40–60 deaths per year in the US were attributed to the use of ethylene glycol as a suicidal agent and as a substitute for ethanol.[6] Case series of suicides using ethylene glycol as the agent were reported in the US (12 cases with 6 deaths) during 1978[7] and in Sweden (36 cases with 6 deaths) during 1987.[8] In 1997, the American Association of Poison Control Centers Toxic Exposure Surveillance System received reports on 4867 exposures to ethylene glycol.[9] The vast majority (about 92%) of these exposures was unintentional and about 1/3 of the exposures to ethylene glycol involved children (<18 years old). There were 21 fatalities among the reported cases. In addition, ethylene glycol intoxication is a common cause of poisoning in small animals brought to veterinarians,[10] and an occasional cause of intoxication in wild animals.[11]

Table 1

Indications for Treatment of Ethylene Glycol Poisoning with an Antidote

Criteria
1. Documented plasma ethylene glycol concentration >20 mg/dL.*
OR
2. Documented recent (hours) history of ingesting toxic amounts of ethylene glycol and osmol gap >10 mosm/L.†
OR
3. History or strong clinical suspicion of ethylene glycol poisoning *and* at least two of the following criteria:
A. Arterial pH <7.3.
B. Serum bicarbonate <20 mEq/L.
C. Osmol gap >10 mosm/L.†
D. Urinary oxalate crystals present.

*There are inadequate data on the exact ethylene glycol concentration at which the use of an antidote is necessary to prevent renal complications. This recommendation is based on limited clinical data and general consensus. †Laboratory analysis by freezing point depression method only.

Physical and Chemical Properties

Ethylene glycol (1,2-ethanediol, CAS No. 107-21-1) is a colorless, odorless, sweet-tasting compound that has a weight of 62.07 g/mole. It is a dihydric alcohol derivative of the aliphatic hydrocarbon ethane (Figure 1). At normal temperatures, ethylene glycol does not vaporize easily as a result of its low vapor pressure (0.6 mm Hg at 20°C) and its low evaporation rate (2.625 times less than ethyl ether). The boiling point of ethylene glycol is 197°C and its pH is neutral. It is miscible in water, lower aliphatic alcohols, and ketones, but is relatively insoluble in hydrocarbons.

Sources

Ethylene glycol is a common constituent of antifreeze and de-icing solutions. Other uses include a stabilizer of moisture content (humectant) in tobacco, baked products, and dentifrices; a constituent of hydraulic brake fluid; a solvent; a stabilizer for foam; a softening agent for cellophane; and a component for chemical synthesis. Accidental ingestions frequently involve the exposure of children to automotive products. Intentional ingestions result from the use of these products as inexpensive substitutes for ethanol or as suicidal agents. Some newer formulations

Table 2

Practice Guidelines for the Treatment of Potentially Serious Ethylene Glycol Ingestions

Treatment	Indications
Gut decontamination	1. Consider gastric aspiration and lavage if <1 h after ingestion. 2. Activated charcoal if mixed ingestion.
Initial laboratory tests	**Blood**: Complete blood count, electrolytes, magnesium, calcium, osmolality, ethanol, and EG. If alcoholic ketoacidosis is suspected, obtain serum lactate, β-hydroxybutyrate. **Urine**: Urinalysis with microscopy for crystals.
General use of an antidote	1. For indications, see Table 1. 2. Administration of the antidote should continue until the EG is nondetectable or EG <20 mg/dL *and* the patient is asymptomatic with normal pH.
Indications for the administration of fomepizole rather than ethanol	1. Ingestion of multiple substances with depressed level of consciousness. 2. Altered consciousness. 3. Lack of adequate intensive care staffing or laboratory support to monitor ethanol administration. 4. Relative contraindication to ethanol.* 5. Critically-ill patient with an anion gap-metabolic acidosis of unknown etiology and potential exposure to ethylene glycol. 6. Patients with active hepatic disease.
Indications for the administration of ethanol rather than fomepizole	1. Fomepizole unavailable.† 2. Hypersensitivity to fomepizole.
Indications for hemodialysis	1. Severe metabolic acidosis (<7.25–7.3) unresponsive to therapy. 2. Renal failure. 3. EG >50 mg/dL unless fomepizole is being administered and patient is asymptomatic with normal arterial pH.
Supportive care	1. Correct fluid deficit. 2. Correct pH <7.3 with intravenous bicarbonate. 3. Replacement of magnesium and administration of thiamine and pyridoxine in depleted patients. 4. Monitor acid-base status; urine output and serum creatinine. 5. Calcium replenishment only for symptomatic hypocalcemia or intractable seizures. 6. Monitor patients receiving an ethanol infusion in an ICU or similar setting capable of providing close monitoring of metabolic acidosis, vital signs, serum abnormalities (glucose, electrolytes), and serum ethanol.

EG = ethylene glycol. *See relative contraindication section under ethanol. †Ethanol should be administered cautiously to young children because of the risk of hypoglycemia.

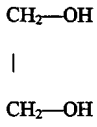

Figure 1. Chemical structure of ethylene glycol.

of antifreeze contain propylene glycol, which is substantially less toxic than ethylene glycol.

Dose-Effect

In the first part of the 20th century, ethylene glycol was considered a relatively innocuous constituent of

pharmaceutical preparations.[12,13] In 1917, Bachem drank 45 mL ethylene glycol[14] and did not suffer any obvious adverse effects from this ingestion. The commonly quoted, minimum lethal dose is 1–1.5 mL/kg or approximately 100 mL for an adult. However, this value is based on an extrapolation from animal studies done during the 1930s and on case histories reported in the 1940s.[3,15,16] The methods used to estimate this minimal lethal dose do not meet current criteria for valid scientific studies.[17,18] Susceptibility to the toxicity of ethylene glycol varies among species. Humans, monkeys, dogs, and cats are highly susceptible to ethylene glycol poisoning, while rats are less susceptible, and mice, guinea pigs, and rabbits are relatively resistant based on interspecies differences in the metabolism of ethylene glycol.[19,20] Consequently, the quantitation of the effect of ethylene glycol, including the effect of fomepizole on ethylene glycol metabolism,[21] is species-dependent. Patients have survived the estimated ingestion of 1 and 2 liters of ethylene glycol when treated within 1 hour.[22,23] The estimated ingestion of 3 liters of ethylene glycol (blood ethylene glycol concentration, 1889 mg/dL) produced nausea, vomiting, metabolic acidosis (pH 7.19), and increased drowsiness on admission 5 hours after ingestion.[24] Although acute nonoliguric renal failure and mild pulmonary edema complicated the hospital course, the patient survived after the prompt initiation of an ethanol infusion, intubation, and hemodialysis.

Toxicokinetics

Absorption

Ethylene glycol is absorbed rapidly in the gastrointestinal tract; however, the percutaneous and pulmonary absorption of ethylene glycol is very limited. In an *in vitro* study of donor skin samples from the thigh of 3 Caucasian males, a dose of 8 μg ^{14}C-labeled ethylene glycol/cm^2 was applied to the skin surface in an acetone vehicle and left for 24 hours.[25] During this time period, the average flux of ethylene glycol for this skin model was 0.09 μg/cm^2/h.

Peak concentrations of ethylene glycol occur 1 to 4 hours after ingestion. There are little data on the pulmonary absorption of ethylene glycol. The low vapor pressure of ethylene glycol virtually excludes exposure to toxicologically significant amounts of vapors at room temperature. Volunteer studies indicate that upper respiratory tract irritation limits exposure to mists of ethylene glycol and there was no evidence of absorption of toxic amounts following exposure to concentrations up to 27 ppm for 4 weeks.[26]

Distribution

Ethylene glycol is highly water-soluble and it distributes evenly and relatively rapidly throughout tissues of the body.[20] The volume of distribution is approximately 0.5–0.8 L/kg.

Metabolism

Figure 2 illustrates the successive oxidation of ethylene glycol to glycoaldehyde, glycolate, and glyoxylate. In the presence of the electron acceptor, nicotinamide adenine dinucleotide (NAD), alcohol dehydrogenase oxidizes ethylene glycol to glycoaldehyde. This zinc-containing enzyme resides primarily in the cytosol of the liver cells. Both ethanol and fomepizole prolong the elimination half-life of ethylene glycol in the blood by competitively inhibiting this step in the pathway (albeit by different mechanisms). The rate-limiting step in the metabolism of ethylene glycol is the conversion of glycolic acid to glyoxylic acid. Aldehyde dehydrogenase converts glycoaldehyde to glycolate rapidly, and consequently little glycoaldehyde appears in the blood during ethylene glycol intoxication. The conversion of glycolate to glyoxylate is slow. The subsequent accumulation of substantial amounts of glycolate in the blood following the ingestion of large amounts of ethylene glycol produces a metabolic acidosis.

Pyridoxine and thiamine are cofactors in some of the metabolic pathways involving glyoxylate (Figures 2). Several pyridoxine-dependent amino acid–glyoxylate aminotransferases catalyze the formation of glycine from glyoxylate. However, glyoxylate accumulates to a much lesser extent compared with glycolate during ethylene glycol poisoning.[27] Therefore, these factors probably do not contribute significantly to the detoxification of ethylene glycol. A small proportion of glyoxylate is metabolized rapidly to oxalate, which quickly precipitates with calcium to form calcium oxalate crystals. These crystals appear throughout the body, primarily in the renal tubules. The oxidation of ethylene glycol to glyoxylate, and subsequently to oxalate, requires the conversion of NAD to NADH. The altered NAD/NADH ratio results in the conversion of pyruvate to lactate and in the production of lactic acidosis.

Elimination

Mechanisms

The liver metabolizes about 80% of the absorbed dose of ethylene glycol. The renal glomeruli filter and then the tubules passively reabsorb approximately 80% of a 1 mg/kg dose of ethylene glycol. The kidneys excrete about

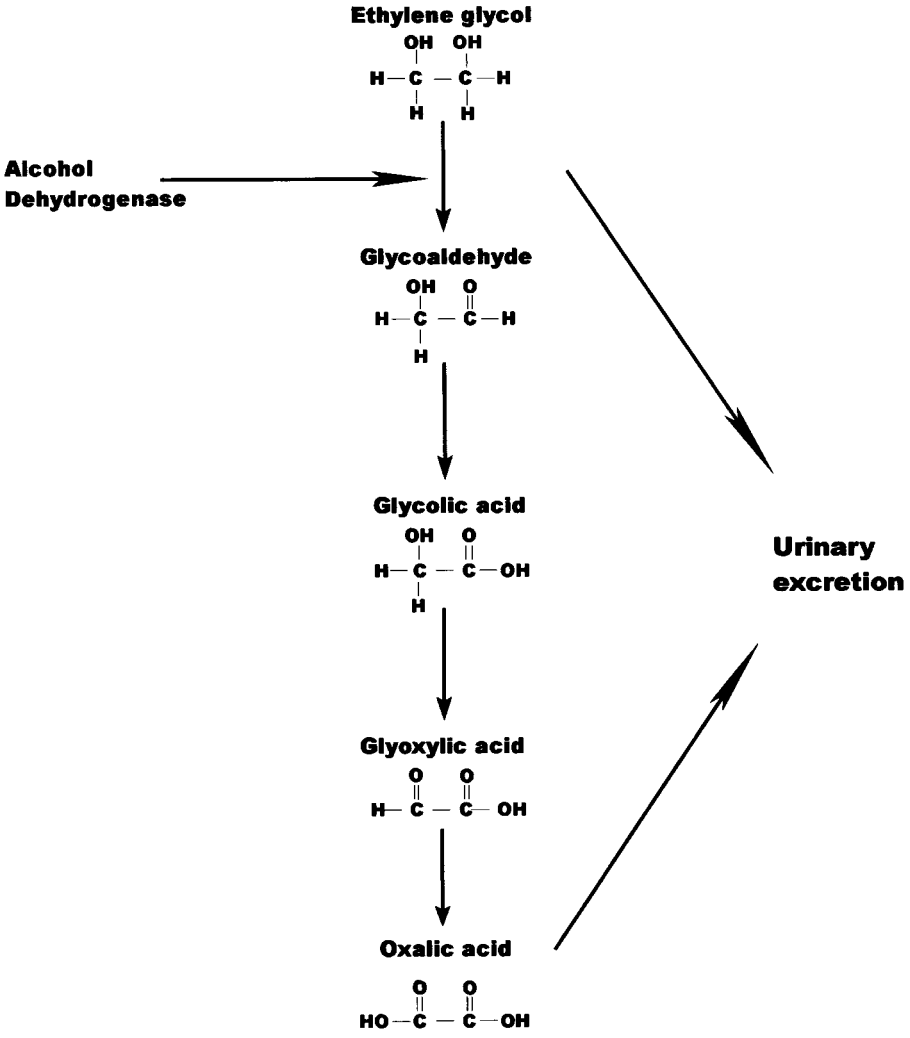

Figure 2. Major pathway for the metabolism of ethylene glycol. The first step in this pathway is catalyzed by alcohol dehydrogenases. Thus, inhibitors of alcohol dehydrogenases prevent the metabolism of ethylene glycol to toxic metabolites.

20% of the dose of ethylene glycol unchanged in the urine. The mean renal clearance of ethylene glycol ranges up to about 27 mL/min depending on renal function.[28] About 1% of the dose of ethylene glycol appears in the urine as the metabolite, oxalic acid. In the rhesus monkey, the kidney excretes 0.5–10% of the dose of ethylene glycol as calcium oxalate.[29] There is little pulmonary excretion of ethylene glycol due to its chemical characteristics of high water solubility and low vapor pressure.

Half-Life

The elimination half-life of ethylene glycol during an episode of poisoning is about 3 hours[30] but it ranges up to 8.6 hours.[31] The presence of ethanol at a concentration of 50–100 mg/dL saturates the active sites of alcohol dehydrogenase and reduces the rate of ethylene glycol metabolism.[32] The affinity of alcohol dehydrogenase for ethanol is substantially greater than the affinity of this enzyme for ethylene glycol. In 0.1 M pyrophosphate buffer (pH 9.0 at 25°C), horse liver alcohol dehydrogenase has a K_m for ethanol of 0.8 mM and for ethylene glycol of 53 mM.[33] The presence of ethanol concentrations of 100 mg/dL prolongs the elimination half-life of ethylene glycol 5-fold to approximately 17–18 hours.[30] Similar prolongation of the half-life of ethylene glycol occurs during treatment with fomepizole. During the META study of patients treated with fomepizole, the ap-

parent half-life of ethylene glycol in patients treated with fomepizole was approximately 20 hours.[34] A fomepizole plasma concentration of 0.8 μg/mL was sufficient to inhibit alcohol dehydrogenase and this was exceeded by the conventional dosing used in the META study.[34]

Pathophysiology

Mechanism of Toxicity

Gastrointestinal Tract

Ethylene glycol is a gastric irritant. Calcium oxalate deposits and focal hemorrhages in the intestinal mucosa also produce irritation of the gastrointestinal tract.

Central Nervous System

Ethylene glycol produces the initial inebriation associated with intoxication. Glycoaldehydes, glycolic acid, and glyoxylic acid may contribute directly to central nervous system (CNS) depression; however, animal studies by McChesney and colleagues[35] and by Clay and Murphy[36] have shown that only glycolic acid reaches high concentrations during ethylene glycol intoxication. Because the average half-life of ethylene glycol is approximately 3 hours, persistent stupor or coma probably results from a metabolic encephalopathy (acidosis, electrolyte imbalance, hypoxemia) and from cerebral edema.[37] Hypocalcemia may contribute to the development of seizures.

Kidney

Serious ethylene glycol poisonings usually produce reversible oliguric or anuric renal failure. The deposition of calcium oxalate crystals in the epithelium of the proximal renal tubules contributes to the development of renal failure, although only a small portion of ethylene glycol is converted to oxalate.[38] The deposition of calcium oxalate crystals also produces hydronephrosis.[39] However, the formation of oxalate crystals does not fully explain the renal toxicity that results from ethylene glycol intoxication. Other suggested mechanisms of renal toxicity involve direct cytotoxicity. Although the exact mechanism of renal toxicity is unclear, toxic metabolites (e.g., glycolate) of ethylene glycol probably contribute to the development of acute tubular necrosis, primarily in the proximal tubules.[40]

Heart

Autopsies of patients who die from ethylene glycol poisoning demonstrate the deposition of calcium oxalate crystals in the myocardium along with interstitial edema and focal hemorrhage, but the contribution of these changes to myocardial dysfunction remains unclear.[41,42] Hypocalcemia may contribute to the development of dysrhythmias and negative inotropic effects. Profound metabolic acidosis also contributes to myocardial depression.

Metabolic Disturbances

The anion gap metabolic acidosis results primarily from the formation of glycolic acid and, to a much lesser extent, from the formation of lactic acid.[43] The rate-limiting step in the metabolism of ethylene glycol is the conversion of glycolate to glyoxylate. This reaction is saturable and the accumulation of glycolate correlates well with the increasing anion gap and the reduction of the serum bicarbonate concentration.[36] Glyoxylate accumulates at a much lower concentration compared with glycolate,[44] and the contribution of glyoxylate to toxicity and the anion gap is probably small.[45] For patients with severe metabolic acidosis during ethylene glycol intoxication, the oxalate concentrations are low ($<$0.33 mmol/L) and oxalate does not appear to contribute significantly to the anion gap.[46] The oxidative metabolism of ethylene glycol depletes the oxidized form of nicotinamide-adenine dinucleotide (NAD^+) and reduces the NAD^+/NADH ratio, resulting in the inhibition of the citric acid cycle and the accumulation of lactic acid. The production of formate during the metabolism of ethylene glycol does not contribute significantly to the development of metabolic acidosis. Hypocalcemia may result from chelation of calcium by oxalate,[22] although there are scant data available to support this hypothesis.

Pathological Findings

The classical pathologic findings of ethylene glycol poisoning are acute tubular necrosis and the presence of calcium oxalate crystals in the kidneys.[47] Nonspecific gross findings include generalized congestion in the leptomeninges, brain, lungs, and abdominal organs. Histological examination of renal tissue from patients with ethylene glycol intoxication reveals widespread necrosis of the renal tubular epithelium and deposition of calcium oxalate crystals in tubular lumina, but the basement membranes and glomeruli remain intact.[48,49] The proximal convoluted tubules are dilated with flattening or vacuolization of the epithelium.[50] Although degeneration of the distal tubules commonly occurs, the damage is less compared with the damage to the proximal tubules. The fact that the amount of renal damage does not correlate with the number of crystals deposited in the kidney suggests

that a direct toxic effect of glycolate or another metabolite may contribute to the renal dysfunction.[51] Marked edema of the brain and lungs may occur along with perivascular extravasation of erythrocytes and lymphocytic or neutrophilic infiltration. Diffuse petechial hemorrhages appear in the brain, pleura, lungs, pericardium and the heart along with cloudy swelling of the heart, and kidneys.[42] Deposition of calcium oxalate crystals occurs in the meningeal vessels, brain, lungs, heart, and spleen.[41]

Clinical Presentation

Renal failure is the most common serious manifestation of ethylene glycol poisoning and hepatic damage is usually minimal. In 1950, Kahn and Brotchner described the following 3 classical stages of ethylene glycol poisoning: 1) neurological, 2) cardiopulmonary, and 3) renal.[38,52] Although these stages are useful theoretical descriptions of ethylene glycol poisoning, the onset and progression of the clinical course is frequently not consistent or predictable. Consequently, one stage may predominate while another stage may be absent. Frequently, patients who present many hours after ingestion are comatose with respiratory distress and renal insufficiency.[53] The severity of each stage and the progression of the clinical course through each stage depend on the amount ingested, the coingestion of ethanol, and the timing of medical intervention.[54] The following clinical findings indicate a severe intoxication when present at admission: hyperkalemia, severe acidosis, seizures, and coma.[55]

Toxicity typically resolves completely after medical treatment, even after profound metabolic acidosis or severe neurological dysfunction.[56] Although renal function usually returns to normal following ethylene glycol intoxication, hemodialysis may be required for months and some renal damage may persist.[57]

Several case reports have described the development of cranial nerve deficits late in the clinical course of ethylene glycol poisoning. Berger and Ayyar described the first case of delayed cranial neuropathies during ethylene glycol intoxication in 1981.[58] Since that time, other cases have been reported that involve cranial nerves II, V, VII, VIII, IX, X, and XII.[59–61] Typically, these patients ingest large (>100 mL) quantities of ethylene glycol, present late in the course of poisoning, and require hemodialysis. The initial onset of the cranial neuropathy is late (5–20 days after ingestion). Bilateral facial neuropathy was present in almost all cases. No abnormalities were present on CT scans of the head, but MRI findings were consistent with local infiltration secondary to the deposition of calcium oxalate crystals.[62] Delayed cranial neuropathy developed in this patient despite adequate supplementation of thiamine and pyridoxine. Recovery was slow in the other patients; however, complete clinical resolution occurred after approximately 1 year.

Stage 1: Neurological (0.5–12 Hours After Ingestion)

Ethylene glycol produces transient inebriation and euphoria that occur within the first several hours after ingestion in a pattern similar to ethanol intoxication, but the odor of alcoholic beverages is absent. These effects result from the parent compound, ethylene glycol. Gastrointestinal symptoms (e.g., primarily nausea and vomiting) result from the direct irritation of ethylene glycol. As the metabolism of ethylene glycol proceeds, a metabolic acidosis develops and CNS depression replaces the initial symptoms of inebriation. Typically, the symptoms associated with the toxic metabolites of ethylene glycol appear 4–12 hours after ingestion. The coingestion of substantial amounts of ethanol may delay the onset of these symptoms to the later part of this range, depending on the dose of ethanol ingested. In cases of more severe poisoning, the alteration of consciousness progresses to coma, associated with hypotonia, hyporeflexia, and occasionally seizures and meningismus. Cerebral edema, considered secondary to cytotoxic damage and to the deposition of calcium oxalate, contributes to CNS depression. Additional neurological symptoms may include nystagmus, ataxia, ophthalmoplegias, and myoclonic jerks. The optic fundus is usually normal, although occasionally the presence of papilledema may confuse the clinical presentation with that of methanol poisoning.

Stage 2: Cardiopulmonary (12–24 Hours After Ingestion)

Tachycardia and mild hypertension occur often. During a serious poisoning, a severe metabolic acidosis with compensatory hyperventilation develops along with multiple organ failure. Hypoxia may result from aspiration of gastric contents, congestive heart failure, or adult respiratory distress syndrome (ARDS).[63] Most deaths occur during this stage.[64]

Stage 3: Renal (24–72 Hours After Ingestion)

This stage is characterized by oliguria, flank pain, acute tubular necrosis, renal failure, and rarely bone marrow suppression.[65] In severe poisoning, renal failure appears early and progresses to anuria. The presence of renal dysfunction may require the use of hemodialysis for

several months. Recovery of renal function is usually complete. However, renal damage may be permanent, although chronic hemodialysis or renal transplantation is rarely necessary. Serious hepatic damage seldom occurs.

Differential Diagnosis

The following combination of signs and/or laboratory findings suggests ethylene glycol toxicity: 1) inebriation without the odor of ethanol, 2) metabolic acidosis with a large anion gap, and 3) an altered mental status, osmolal gap, and calcium oxalate crystals with hypocalcemia. In the absence of diabetic or alcoholic ketoacidosis, the presence of both an osmolal gap and an anion gap strongly suggests either ethylene glycol or methanol poisoning. The clinical presentation of methanol poisoning is similar to the clinical presentation of ethylene glycol poisoning, but visual abnormalities and papilledema suggest the former. In the absence of hypotension, alcoholism, renal failure, seizures, and diabetes, the presence of an anion gap suggests the presence of a toxic substance, such as ethylene glycol, propylene glycol, methanol, iron, or salicylates.

Laboratory

SI Units

1 mg/dL = 0.161 mmol/L = 161 μmol/L
1 mmol/L = 62 mg/L = 6.2 mg/dL

Abnormalities

Although the combination of an osmolal gap and an anion gap is strongly suggestive of ethylene glycol or methanol intoxication, certain clinical conditions may also produce these abnormalities. Examples include diabetic ketoacidosis (accumulation of acetone, acetoacetate, β-hydroxybutyrate), alcoholic ketoacidosis (primarily β-hydroxybutyrate), multiple organ failure, chronic renal failure, and critical illness.[66–68]

Osmolal Gap

Osmolality (osmoles per kilogram solvent) and osmolarity (osmoles per liter of solution) represent a measure of the number of particles dissolved in solution. The osmolal gap is an estimate of the unmeasured, osmotically active constituents in the serum. This gap consists primarily of calcium, calcium anions, proteins, and lipids. In healthy individuals, Equation 1 estimates the serum osmolarity (O_C) based on the concentrations of sodium, glucose and urea nitrogen (BUN) in SI units (mmol/L).

$$\text{Calculated osmolarity } (O_C) = (1.86[Na] + [BUN] + [glucose]) \div 0.93 \quad (1)$$

To use traditional units, divide the BUN concentration in mg/dL by 2.8 and the glucose concentration in mg/dL by 18. The measured osmolality (O_M) normally is about 270–290 mOsm/kg H_2O. Osmolarity or osmolality should be measured by the *freezing point depression* method even though ethylene glycol is not very volatile because the vapor pressure method underestimates the contribution of volatile alcohols (ethanol, isopropanol, methanol, propylene glycol).[69,70] The difference between the measured and calculated osmolality is the osmolal gap (O_G) as defined by Equation 2. Normally, the value of the gap using Equation 1 in the calculation of Equation 2 is 10–15 mOsm/kg H_2O. The reference range for the osmolal gap depends on the variability of the laboratory equipment (i.e., coefficient of variance) and the exact reference range is specific to the individual hospital.[71] The presence of an elevated osmolal gap suggests that significant concentrations of ethylene glycol, propylene glycol, methanol, ethanol, isopropanol, or acetone may be present. Early in the course of an ethylene glycol poisoning, the osmolal gap usually exceeds 20 mOsm/kg H_2O, but late in the course, the osmolal gap may be normal.

$$O_G = O_M - O_C \quad (2)$$

The contribution of metabolites of ethylene glycol to the osmolal gap is small, and ethylene glycol accounts for the majority of the osmolal gap produced, following the ingestion of ethylene glycol. Consequently, the osmolal gap may be transient because of the relative short plasma half-life (approximately 3 hours) of ethylene glycol and the limited osmotic activity of the metabolites of ethylene glycol. The maximum osmolal gap occurs following the peak absorption of ethylene glycol, prior to metabolism. As the metabolism of ethylene glycol proceeds, the osmolal gap decreases and the anion gap increases. Consequently, late in the course of ethylene glycol poisoning, the osmolal gap does not reflect the severity of the poisoning.[72,73]

The contribution of ethylene glycol to the osmolal gap is relatively small compared with other alcohols. A serum ethylene glycol concentration of 50 mg/dL, which is associated with a serious ingestion of ethylene glycol, produces an 8–10 mOsm rise in the osmolal gap. Several studies of patients using standard calculations of the osmolal gap indicate that the 95% confidence limit for the osmolal gap includes negative values.[74,75] Therefore, the presence of an osmolal gap supports the diagnosis of eth-

ylene glycol poisoning, but the absence of an osmolal gap does not exclude serious poisoning.

Other compounds may contribute to the osmolal gap (Table 3). Erroneously elevated osmolal gaps may result from the presence of one of the following in the blood: spurious hyponatremia secondary to hyperlipidemia or to hyperproteinemia, the presence of endogenous solutes (e.g., amino acids during end organ failure), sorbitol, diatrizoate (IVP dye), glycerin, fructose, propylene glycol, or mannitol.

Anion Gap

The plasma is in a state of electrical neutrality with the concentration of cations being equal to the concentration of anions. The anion gap is the difference between the sum of the measured cations and the sum of the measured anions. Under normal circumstances, this gap represents negatively charged proteins (albumin), fatty acids, and inorganic anions (sulfates, phosphates). Routinely, laboratories measure sodium and potassium, which together account for about 95% of the extracellular cations, as well as chloride and bicarbonate, which together represent about 85% of the extracellular anions. The anion gap represents unmeasured anions. Normally, the anion gap is about 12–16 mmol/L, but the actual levels vary between laboratories depending on the accuracy of laboratory measurements. The anion gap is defined by

$$\text{Anion Gap (AG)} = [(Na^+ + K^+) - (HCO_3^- + Cl^-)] \quad (3)$$

The metabolism of ethylene glycol produces organic acids, and consequently the size of the anion gap depends both on the amount of ethylene glycol ingested and on the time since ingestion. Initially, serum bicarbonate concentrations fall as the metabolism of ethylene glycol proceeds. Therefore, a significant metabolic acidosis may appear before the anion gap develops. Glycolic acid is the major constituent (i.e., approximately 96%) of the anion gap[46] and the severity of the metabolic acidosis correlates with the serum glycolate concentration.[72] The concurrent ingestion of ethanol with ethylene glycol delays the metabolism of ethylene glycol to its acid metabolites and therefore the appearance of the anion gap. In the absence of renal failure, hypotension, diabetes, seizures, and alcoholism, the presence of an elevated anion gap is suggestive of the ingestion of toxic substances, such as methanol, ethylene glycol, propylene glycol, iron, or salicylates.

Most patients who have a metabolic acidosis from ethylene glycol poisoning develop a metabolic acidosis with a compensatory respiratory alkalosis. However, several rare conditions may obscure the anion gap during ethylene glycol poisoning despite the presence of an acidemia. Examples include multiple myeloma and the simultaneous ingestion of bromides that erroneously reduces the anion gap.[76] Most clinical laboratories do not distinguish bromide from chloride. The ingestion of lithium carbonate provides additional bicarbonate, and thus this ingestion also reduces the anion gap when coingested with ethylene glycol.[77]

Urine

The presence of two forms (monohydrate, dihydrate) of calcium oxalate crystals in the urine provides supportive evidence for ethylene glycol poisoning. The presence of these two hydrated forms of calcium oxalate alone is not specific for ethylene glycol poisoning because they are found naturally in plant tissues. The predominant type of crystal is the monohydrate form (whewellite), which may be confused with hippurate crystals.[78,79] During periods of high concentrations of urinary oxalate, these crystals may be present in the dihydrate form (weddel-

Table 3

Approximate Osmolal Contribution of Some Alcohols and Ketones

Compound	Concentration (mg/dL)	Osmolal Contribution (mOsm/kg H_2O)
Propylene glycol	100 (13 mmol/L)	13
Ethylene glycol	100 (16 mmol/L)	16
Isopropanol	100 (17 mmol/L)	17
Acetone	100 (18 mmol/L)	18
Ethanol	100 (22 mmol/L)	22
Methanol	100 (34 mmol/L)	34

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lite), which is more specific for ethylene glycol toxicity than the monohydrate form. These crystals appear after a latent period of about 4–8 hours[80,81] and may be detectable up to 40 hours postingestion in the absence of ethanol.[82] In the presence of renal failure, these crystals may persist in the urine for 6–10 days.[83,84] On admission, up to about 50% of patients poisoned with ethylene glycol have calcium oxalate crystals in their urine, and the percentage increases if the urinalysis is repeated over the course of the poisoning.[85] The presence of hypocalcemia *and* calcium oxalate crystals in the urine is highly suggestive of ethylene glycol poisoning. Although oxalate is normally a minor metabolite of ethylene glycol metabolism, oxalate crystals in the urine are a common, but not invariable, feature of ethylene glycol intoxication.[86] The amount of oxalate crystalluria does not correlate with the amount of ethylene glycol absorbed.[55] Repeat urinalysis may be necessary to identify calcium oxalate crystals in the urine, particularly when the patient presents early in the course of the poisoning. Healthy individuals, who ingest excessive amounts of vitamin C or foods (e.g., cocoa, garlic, rhubarb, tea, tomatoes, spinach) that contain high concentrations of oxalates, may develop crystalluria without renal dysfunction.

When viewed through polarized light, calcium oxalate crystals are birefringent, variegated, and pleomorphic. There are two forms of urinary calcium oxalate crystals: the octahedral or tent-shaped form of the dihydrate crystals, and the prism or dumbell-shaped monohydrate form.[87]

The latter form is stable under normal physiologic conditions and the dihydrate form appears only during high urinary calcium and oxalate concentrations, as seen in ethylene glycol poisoning. The dihydrate form can transform into the monohydrate form.[88] The monohydrate form of oxalate crystals is easily misidentified as hippuric acid crystals. However, X-ray diffraction definitively separates these two types of crystals.

Other reported features of ethylene glycol poisoning include hematuria, proteinuria, and the inability to concentrate urine. Because antifreeze usually contains sodium fluorescein as a marker for detecting radiator leaks, the use of a Wood's lamp can occasionally detect the presence of sodium fluorescein in the urine, in the lavage fluid, or on the skin.[89]

Blood

Hypocalcemia may occur as a result of the formation of calcium oxalate crystals and hypocalcemia is manifested by QT prolongation on the ECG. Hyperreflexia and muscle spasms may result. Myalgias, elevated serum creatinine concentrations, and increased serum creatinine phosphokinase concentrations may also develop.[43] Leukocytosis is common.

Radiography

Frequently, the cranial CT is normal despite the presence of neurological signs.[90] The CT scan of the head may demonstrate evidence of cerebral edema with compression of the supratentorial ventricular system. Reversibility of hypodense regions (thalamus, basal ganglia, pons, corpora quadrigemina, and basal portions of the temporal lobes) in a patient who ingested ethylene glycol was consistent with meningoencephalitis.[91] A patient who ingested ethylene glycol became comatose with flaccid quadriplegia.[56] The cranial CT demonstrated hypodense areas extending from the upper brain stem to the basal ganglia along with signs of diffuse brain edema. The patient recovered completely within 6 weeks and the repeat cranial CT was normal.

Serum Ethylene Glycol Concentrations

The lack of correlation between the serum ethylene glycol concentration and clinical symptoms results from the rapid conversion of the parent compound to toxic metabolites. The severity of an ingestion of ethylene glycol depends on the absorbed dose (i.e., area under the curve), which roughly correlates to the peak ethylene glycol concentration. However, patients frequently present late in the course of a severe ethylene glycol poisoning, when the serum ethylene glycol concentrations are low as a result of the conversion of ethylene glycol to its toxic metabolites. These patients usually have a significant metabolic acidosis. Although the acidosis does not correlate with the serum ethylene glycol concentration, the severity of the metabolic acidosis does correlate with the rise of serum creatinine 72 hours after ingestion.[92] Recovery has occurred with aggressive treatment in the presence of ethylene glycol concentrations of 145 mg/dL (8-hour concentration) and 560 mg/dL (1-hour concentration).[23,93] Reported serum ethylene glycol concentrations in survivors that were treated promptly included concentrations of 650 mg/dL (146.1 mmol/L)[94] and 1889 mg/dL,[24] whereas concentrations between 98 and 775 mg/dL were reported in fatalities.[23,83,95] Elevated glycolic acid and reduced bicarbonate concentrations correlate better with the severity of the intoxication than to the serum ethylene glycol concentration because these concentrations reflect the effect of the toxic metabolites. In a study of 19 patients who ingested ethylene glycol and

were treated with fomepizole, no patient with an initial glycolate concentration <10 mM developed signs of renal dysfunction.[34]

Analytical Methods

Ethylene Glycol

The method of choice for analyzing ethylene glycol is gas chromatography with flame ionization detection of ethylene glycol or its boronic ester derivative.[31,96] Appropriate internal standards include 1,3-propanediol or 1,2-butanediol, but not propylene glycol. The IV use of medications (e.g., diazepam, phenytoin), which contain propylene glycol, may produce false positive results for ethylene glycol. Confirmation by mass spectrometry is recommended because of the potential confusion of propionic acid, 2,3-butanediol, and methanol-like products present in the sera of diabetic patients with ketoacidosis.[97] The analysis of ethylene glycol requires a separate, dedicated gas chromatography column, which is expensive, and therefore most clinical laboratories send the blood samples to reference laboratories for analysis of ethylene glycol. Significant delays in treatment will occur if the physician withholds treatment until the reference laboratory reports the results.

There are screening assays for ethylene glycol that utilize glycerol dehydrogenase.[98] During the oxidation of ethylene glycol, this enzyme produces NADH, which is measured spectrophotometrically. Crossreactions occur with glycoaldehyde and glycerol, but not with methanol, isopropanol, ethanol, acetaldehyde, lactate, or other metabolites of ethylene glycol. Although the concentrations of glycoaldehyde and glycerol are usually low, interference may occur in critically ill patients with high serum glycerol (i.e., infusion of glycerol-containing medications) or elevated serum lactic acid concentrations.[31] Measurement of serum ethylene glycol concentrations is not a routine part of toxicology screens.

Fomepizole

High-performance liquid chromatography is a rapid method for the determination of fomepizole in the plasma and in dialysate.[99,100] The limit of quantitation is 0.3 mg fomepizole/L plasma and the method is linear up to 30 mg/L.[101] Other methods include gas chromatography with nitrogen-sensitive detection[102] and mass fragmentography.[103] This method is linear over the range of 25–1000 ng/mL plasma and 0.5–5 μg/mL urine. The between-day coefficient of variation was <6%. The use of fomepizole concentrations is not a routine part of the management of cases of ethylene glycol poisoning.

Ethanol

The reference method for the determination of ethanol is headspace gas chromatography. However, most clinical laboratories use enzymatic ethanol assays to detect and to quantify the presence of ethanol in serum samples. These simple, rapid assays utilize the oxidation of ethanol to acetaldehyde by alcohol dehydrogenase with the concurrent reduction of nicotinamide adenine dinucleotide (NAD) to NADH. The absorbance at 340 nm due to NADH formation correlates with the serum ethanol concentration. Other enzymatic reactions (e.g., serum lactate, lactate dehydrogenase) that use NAD as a coenzyme and generate NADH may interfere with the determination of ethanol.[104] Plasma ethanol concentrations are similar to serum ethanol concentrations, but the ethanol concentration in blood cells is lower than in the plasma. Consequently, the whole-blood ethanol concentration is lower (approximately 15%) than the serum ethanol concentration.[105]

Treatment

Stabilization

The initial evaluation should be directed toward the evaluation and correction of immediate life-threatening complications (i.e., airway, breathing, circulation). The most common serious complications of ethylene glycol poisoning are CNS depression, acute renal failure, and metabolic acidosis. IV glucose (50% glucose 50 mL or 25% glucose 2 mL/kg body weight in children) should be administered to patients who have altered mental status and suspected hypoglycemia unless the rapid glucose screen demonstrates an adequate glucose concentration. Frequently, patients who ingest ethylene glycol are alcoholics. These patients should receive thiamine 100 mg intravenously as well as multivitamin supplementation. Fluid resuscitation should be guided by clinical assessment of volume status and the serum creatinine concentration in order to prevent fluid overload in those patients who present with renal dysfunction.

Seizures should be treated with standard doses of IV benzodiazepines (diazepam, lorazepam) and, if needed, IV phenytoin or fosphenytoin. The development of persistent seizures suggests the presence of hypocalcemia, particularly if large amounts of sodium bicarbonate are required to treat the metabolic acidosis. The administration of IV calcium is not recommended routinely to correct hypocalcemia because of the potential to increase

the formation of calcium oxalate crystals. However, if seizures persist despite the administration of adequate doses of anticonvulsants, the administration of 10–20 mL (0.2–0.3 mL/kg) 10% calcium gluconate as a slow IV infusion is an option, particularly in the presence of a prolonged Q-T interval. Large amounts of sodium bicarbonate may be necessary in the first several hours to correct the metabolic acidosis. Serum sodium, acid-base status, and fluid balance should be monitored closely.

Gut Decontamination

The efficacy of activated charcoal, cathartics, or gastric lavage following the ingestion of ethylene glycol has not been documented. The rapid absorption of ethylene glycol suggests that gastrointestinal decontamination (i.e., gastric aspiration and lavage) may be effective only within the first hour after ingestion.[106] The administration of syrup of ipecac is contraindicated because of the risk of CNS depression. Activated charcoal does not bind clinically significant amounts of ethylene glycol, and therefore the use of activated charcoal is not indicated following the ingestion of ethylene glycol unless indicated by the coingestion of other drugs.[107,108]

Antidotes

Supportive care is the cornerstone of managing all poisoned patients. Ethanol has been the traditional antidote for ethylene glycol intoxication, even though it has not been studied prospectively and the US FDA has not approved ethanol for the treatment of ethylene glycol poisoning. The US FDA recently approved the use of fomepizole (Antizol) as an effective antidote for ethylene glycol intoxication. There are no clinical studies that directly compare the efficacy of fomepizole with that of ethanol.

Ethanol

Ethanol has been the recommended antidote for ethylene glycol intoxication since Wacker *et al*. published their experience with its use in 1965.[109] Although ethanol has also been used as an antidote for methanol poisoning since the 1940s,[110] the FDA has not approved its use for either methanol or ethylene glycol poisonings.

Formulation Ten percent (volume/volume) IV solutions of ethanol are difficult to obtain commercially. Use of a 5% solution of ethanol requires administration of large volumes of fluid. If available, a 95% solution of ethanol may be diluted to 10% by removing 50 mL of fluid from 1 liter of 5% ethanol in dextrose 5% (D_5A_5) and replacing the extracted fluid with 50 mL of 95% ethanol. Alternately, withdrawing 100 mL of fluid from 1 liter of 5% dextrose and replacing the extracted fluid with 100 mL of absolute ethanol produces a 10% ethanol solution. Prior to dilution, the ethanol should be purified through a micron filter because these solutions are not pyrogen-free. Denatured ethanol should not be used. Ethanol may be administered orally as a 20% pharmaceutical preparation or as an alcoholic beverage.

Pharmacokinetics Ethanol is absorbed rapidly from the gastrointestinal tract primarily from the duodenum. Factors that prolong gastric emptying, including the presence and type of food, reduce and delay ethanol absorption. Ethanol distributes into the total body water. The approximate volume of distribution (V_d) is 0.6–0.7 L/kg. Women have a slightly smaller V_d because the average woman has less water and more fat compared with the average man or child.[111,112] Ethanol crosses the placenta and the blood-brain barrier rapidly. The liver metabolizes 90–98% of an absorbed dose of ethanol, while the kidneys and lungs excrete most of the remaining dose of ethanol unchanged. Zero-order kinetics characterize the hepatic metabolism of ethanol except at very low or very high concentrations.[113,114] The rate of metabolism depends on a variety of factors, including age, chronic use of ethanol, ethanol concentration, and type of blood specimen (e.g., whole blood vs serum). Typical ethanol elimination rates average about 15–20 mg/dL/h in healthy adults with a range of 10–34 mg/dL/h.[115] The ethanol elimination rate is higher in alcoholics compared with nonalcoholic adults.

Mechanism of Action Alcohol dehydrogenase has a higher affinity for ethanol than for ethylene glycol,[116] and thus ethanol competitively inhibits the metabolism of ethylene glycol to its toxic metabolites by blocking the receptor sites of alcohol dehydrogenase. Ethanol therapy has been used successfully for many years to reduce the formation of toxic metabolites and indirectly to increase the renal elimination of ethylene glycol. However, standard doses of ethanol may not completely block metabolism of high concentrations of ethylene glycol. Despite the presence of therapeutic doses of ethanol and the use of hemodialysis, renal failure may develop in patients who ingest large amounts of ethylene glycol. A 28-year-old male presented with classic signs of severe ethylene glycol poisoning (arterial pH = 6.99, urinary calcium oxalate crystals, altered consciousness) despite the presence of a serum ethanol concentration of 120 mg/dL on admission.[117] The use of hemodialysis beginning 4 hours after activation of the 911 call and the continuation of an etha-

nol infusion did not prevent the development of anuria on the 2nd day of hospitalization.

Indications Ethanol infusions are not the sole therapy or the sole antidote for ethylene glycol intoxication.[43] The clinical course of each patient should be evaluated for factors which favor the use of one antidote over another (Table 2). The presence of acidemia following ethylene glycol intoxication indicates the presence of toxic metabolites and hemodialysis may be indicated to correct the acidosis and to prevent the development of renal failure.

General indications for the use of an antidote are listed in Table 1. Ethanol should be administered as soon as possible because the elimination half-life of ethylene glycol is approximately 3 hours. The administration of fomepizole should be considered instead of ethanol for ethylene glycol intoxication, particularly if the patient develops altered consciousness, seizures, or a significant metabolic acidosis. A case report suggests that therapeutic concentrations of ethanol may not block the formation of toxic metabolites from very high concentrations of ethylene glycol,[117] and use of fomepizole in this situation may offer a theoretical advantage over the use of ethanol.

Cautions

1. Relative contraindications

Ethanol should be used with caution in patients who recently have ingested disulfiram or drugs that produce CNS depression. Similar reactions may occur following the co-administration of metronidazole or chlorpropamide. Ethanol should be used with caution in patients with hepatic disease and the oral administration of ethanol should be avoided when there is a recent history of gastrointestinal ulcers. In patients with a history of alcohol addiction, fomepizole therapy may be preferable to the use of ethanol.

2. Precautions

a. Drug interactions

Flushing and hypotension may occur following the administration of ethanol to patients on disulfiram therapy. For patients who have ingested ethanol in addition to ethylene glycol, the loading dose of ethanol should be reduced accordingly. Ethanol is a CNS depressant and the coingestion of other CNS depressants (e.g., opioid analgesics, antihistamines, sedative-hypnotics, muscle relaxants, anticonvulsants, antidepressants) would be expected to enhance the depressant effect of ethanol. Ethanol may cause orthostatic hypotension in patients who use vasodilator agents.

b. Pregnancy

The treatment of ethylene glycol poisoning with ethanol is short-term (i.e., several days). The adverse reproductive effects (e.g., fetal alcohol syndrome) associated with ethanol are not expected to occur following the use of ethanol as an antidote for ethylene glycol poisoning during the 2nd and 3rd trimester. The use of any alcohol during the 1st trimester is more controversial because of the association of fetal alcohol syndrome with peak ethanol concentrations during a short period of vulnerability during organogenesis.

c. Children

There are few data on the complications of the ethanol infusions in children. Children are more susceptible to the development of hypoglycemia during ethanol intoxication compared with adults.[118] Neither ethanol nor fomepizole is approved for use during ethylene glycol intoxication in children.

Administration The infusion of ethanol requires close monitoring (i.e., every 1–2 hours) of serum ethanol concentrations until the serum ethanol concentration reaches a steady state of 100–150 mg/dL. Serum ethanol concentrations may change after the achievement of steady state concentrations, and therefore the serum ethanol concentration should be monitored every 2–4 hours during this period. Variability in individual metabolic rates and the rate-limited kinetics of ethanol may cause large increases in the serum ethanol concentration after only small changes in the infusion rate. Consequently, any change in the infusion rate (e.g., initiation of treatment, adjustment of ethanol dose, hemodialysis) requires careful monitoring (i.e., every 1–2 hours) of the serum ethanol concentration until the serum ethanol concentration reaches a steady state concentration within the therapeutic range. IV ethanol should be administered through an infusion pump and the patient should be monitored in an intensive care setting in order to observe the patient closely for signs of CNS and respiratory depression and to monitor the serum ethanol concentration.

The kinetics of ethanol following oral administration are more unpredictable than the kinetics of IV ethanol. Therefore, close monitoring of serum ethanol concentrations is also necessary after oral loading doses and changes in the oral dosage. Because of the hyperosmolarity of loading doses of ethanol, the initial dose of ethanol is administered over 1 hour. For maximum tolerability, the oral solution of ethanol is diluted to 20% ethanol and administered hourly via a nasogastric tube.

Dosage The loading dose is 0.6–0.7 g ethanol/kg. Initially, the serum ethanol concentration should be monitored closely (i.e., every 1–2 hours) in order to ensure that the serum concentration remains in therapeutic range of 100–150 mg ethanol/dL. Theoretically, the amount of ethanol necessary to prevent the formation of toxic metabolites depends on the amount of ethylene glycol present, and therefore relatively higher doses of ethanol may be required for very large ingestions of ethylene glycol. The average maintenance dose is about 110 mg ethanol/kg/h (1.4 mL 10% ethanol/kg/h). The actual dose varies from 66 mg ethanol/kg/h (0.8 mL 10% ethanol/kg/h) for nondrinkers to 154 mg ethanol/kg/h (2.0 mL 10% ethanol/kg/h) for alcoholics as outlined in Table 4. For severe adult poisoning in which medical care will be delayed several hours, the use of approximately four 1-oz oral ''shots'' of 80-proof whiskey before or during transport to the hospital is an option (see Equation 4).

$$\text{Oral loading dose} = \text{g ethanol/mL 80 proof solution} \quad (4)$$

Assuming:

Loading dose for 70 kg patient (g ethanol)

$$= 0.6 \text{ g/kg} \times 70 = 42 \text{ g}$$

Amount (grams) ethanol in 80 proof solution

$$= 0.40 \text{ v/v ethanol} = 0.40 \times 0.79 = 31.6 \text{ g/100 mL}$$

Assuming: 80 proof solution

$$= 40\% \text{ ethanol and specific gravity} = 0.79$$

$$= 42.0 \text{ g} \div \text{amount ETOH in 80 proof solution}$$

$$= \frac{42 \text{ g}}{31.6 \text{ g per 100 mL 80 proof solution}}$$

$$\text{Amount required} = 42.0 \text{ g} \div (31.6 \text{ g} \times 100 \text{ mL})$$

$$= 132.9 \text{ mL} \quad \text{(or about 2 mL/kg body weight)}$$

Ethanol therapy should continue until the ethylene glycol serum concentration is undetectable or <20 mg/dL *and* the patient is asymptomatic with a normal arterial pH. The presence of a metabolic acidosis despite ethylene glycol concentrations <20 mg/dL suggests the presence of substantial concentrations of glycolate or a coexisting process. Based on an elimination half-life of 17 hours for ethylene glycol in the presence of ethanol, approximately 2–3 days are necessary to eliminate ethylene glycol during an ethanol infusion. Table 4 outlines the range of ethanol doses based on *average* pharmacokinetic values and the chronic use of ethanol. The dose for moderate drinkers is about the mean between the value listed for nondrinkers and the value for alcoholics listed in Table 4. The actual amount of ethanol administered depends on the results of frequent monitoring of the serum ethanol concentration. First-pass metabolism reduces the bioavailability of orally administered ethanol and the use of IV ethanol produces slightly higher and earlier peak serum ethanol concentrations compared with the oral route.[119] The clinical significance of these pharmacokinetic differences remains unclear. Low doses of ethanol, food, and chronic ethanol consumption increase first-pass metabolism.[120] However, these effects are usually minor (<10%) following the administration of moderate doses of ethanol after a light meal.[121,122]

Adverse effects Ethanol may cause hypoglycemia, particularly in children and in malnourished patients. The dose required to treat ethylene glycol poisoning will produce clinical signs and symptoms of ethanol intoxication (e.g., inebriation, depression of cortical function, emotional lability, poor coordination, loss of judgment, visual impairment, slurred speech). Therefore, patients should be assisted with any action that requires judgment or coordination. Severe depression of mental status may necessitate intratracheal intubation in order to protect against aspiration and respiratory depression, particularly with the coingestion of another CNS depressant. A 10% solution of ethanol is hyperosmolar (1713 mosM/L) without dilution, and therefore a local phlebitis may develop following the IV use of this solution. The administration of 10% ethanol IV frequently requires central venous access.

Fomepizole (4-Methylpyrazole, 4-MP, Antizol)

Fomepizole is a potent inhibitor of alcohol dehydrogenase. In the 1970s, investigators demonstrated that fomepizole could prevent the metabolic acidosis associated with ethylene glycol poisoning in animals.[19,36,123] The manufacturer recently completed phase III trials for use of this drug in the treatment of methanol poisoning. Other suggested uses for fomepizole that are not approved by the FDA include the following: diethylene glycol toxicity,[27] propylene glycol intoxication,[124] prevention of the disulfiram/ethanol reaction,[125] and the suppression of acetaldehyde accumulation in alcohol-sensitive patients.[126]

Potential advantages of the use of fomepizole compared with ethanol infusions include the following: ease of administration, predictable pharmacokinetics, improved patient safety profile, standardized and less complicated dosing regimen that does not require direct observation and frequent blood monitoring, fewer side effects, and potentially reduced intensive care and hemo-

Table 4

Standard Range of Therapeutic Doses of Ethanol Based on Average Pharmacokinetic Values

	Amount Absolute Ethanol*	Volume (43% Oral Solution)†	Volume (10% IV Solution)‡
Loading dose§	600 mg/kg	1.8 mL/kg	7.6 mL/kg
Standard maintenance dose, Nondrinker	66 mg/kg/h	0.2 mL/kg/h	0.83 mL/kg/h
Standard maintenance dose, chronic drinker	154 mg/kg/h	0.46 mL/kg/h	1.96 mL/kg/h
Maintenance dose during dialysis, nondrinker	169 mg/kg/h	0.5 mL/kg/h	2.13 mL/kg/h
Maintenance dose during dialysis, chronic drinker	257 mg/kg/h	0.77 mL/kg/h	3.26 mL/kg/h

*Specific gravity = 0.79; †equivalent to 86 proof undiluted liquor (34 g ethanol/dL); ‡equivalent to 7.9 g ethanol/dL; §assumes initial ethanol concentration is zero, dose is independent of chronic drinking status. Adapted from Ref 122.

dialysis costs. Fomepizole does not cause CNS depression and the drug has a longer duration of action compared with ethanol. The primary disadvantages of the use of fomepizole are the high acquisition cost and the limited clinical experience. Considering the cost of blood ethanol monitoring and the use of an infusion pump in an intensive care setting, the cost of administering ethanol may be equal to or greater than the cost of using fomepizole for patients who are stable.

Formulation In the US fomepizole is available as a parenteral solution (Antizol) from Orphan Medical (Minnetonka, MN). Each vial contains 1.5 g fomepizole. The solution is a clear-to-yellow, water soluble liquid, which may solidify at room temperature because its melting point is 25°C (77°F). Antizol is the free base form of fomepizole and Antizol has a molecular weight of 82.1 g/mole.

Pharmacokinetics The information on the pharmacokinetics of fomepizole is based on a small number of animal studies, case studies, and human volunteer studies. There are few data on the effect of age, gender, hepatic insufficiency, or renal dysfunction on the pharmacokinetics of fomepizole. Case reports indicate that hemodialysis removes significant amounts of fomepizole. In 2 patients with anuric renal failure due to ethylene glycol poisoning, the removal rates were 50 mg/h and 83 mg/h.[127] The mean dialysances were 117 mL/min and 137 mL/min, respectively.

1. Distribution

Fomepizole distributes rapidly into total body water with a volume of distribution of approximately 0.6–1.0 L/kg. Most patients treated with fomepizole receive concentrations of fomepizole that far exceed the minimally effective concentration (>10 μmol/L or >0.821 mg/L).[128] The fomepizole concentrations in patients enrolled in the META study ranged from 200–400 μmol/L (16.42–32.8 mg/L).[34] An adequate therapeutic serum concentration is 8–25 mg fomepizole/L with concentrations >15 mg (183 μmol) fomepizole/L producing complete inhibition of alcohol dehydrogenase based on clinical trials.[129]

2. Metabolism

Elimination of fomepizole occurs almost exclusively (approximately 97%) by hepatic metabolism.[130] The major metabolite in humans is 4-carboxypyrazole (approximately 80–85% of a therapeutic dose). There are species-related differences in the pharmacokinetics of fomepizole. For example, rats excreted >70% of a dose of 50 mg/kg body weight as 4-hydroxymethylpyrazole and 4-carboxypyrazole.[131] Other minor, inactive metabolites of fomepizole that are found in the urine of humans include **N**-glucuronide conjugates of 4-carboxypyrazole and 4-

hydroxymethylpyrazole. Only 1–3.5% of an administered dose of fomepizole appears unchanged in the urine of healthy volunteers.

3. Elimination

The plasma elimination rate of fomepizole varies with dose and with duration of treatment. At therapeutic concentrations (8.2–24.6 mg/L) fomepizole displays dose-dependent, nonlinear elimination that does not match Michaelis-Mentin kinetics. These complicated kinetics probably result from the action of multiple metabolizing enzymes, some of which are saturable and some of which are inducible. Along with a variety of diverse compounds (ethanol, acetone, isoniazid, pyridine), fomepizole induces the P_{450} mixed function oxidase system, particularly P_{450}-IIE1.[132] The elimination rate of fomepizole increases over the first 30–40 hours after the initial dose. Enzyme induction is complete after this period, and first-order elimination of fomepizole then occurs. The calculation of the plasma half-life is not practical. At therapeutic doses, the apparent rate of elimination is about 5 μmol (0.41 mg)/L/h, and thus a dose of 10 mg/kg is eliminated in approximately 25 hours.[130]

Mechanism of Action Fomepizole is a potent inhibitor of alcohol dehydrogenase in the liver tissue of dogs and monkeys. By increasing the half-life of ethylene glycol in the blood, the administration of fomepizole prevents the formation of toxic metabolites and increases the renal elimination of the parent compound while the blood still contains significant amounts of ethylene glycol.[133] In the monkey model, fomepizole is a more potent inhibitor of liver alcohol dehydrogenase compared with its more toxic parent compound, pyrazole.[134] The competitive inhibition of alcohol dehydrogenase by fomepizole probably results from the formation of an inactive ternary complex between alcohol dehydrogenase and the coenzyme NAD.[135] In studies of rats, fomepizole also inhibits the activity of the cytochrome P_{450}-dependent monooxygenase system.[136,137] A blood concentration of 10 μM fomepizole produces constant inhibition of alcohol dehydrogenase activity in monkeys.[138] Based on *in vitro* studies in human liver tissue, the potency (K_i) of fomepizole to inhibit alcohol dehydrogenase activity in humans is in the range of 1 μM.[135]

A study in dogs suggested that fomepizole is a more effective inhibitor of alcohol dehydrogenase compared with ethanol.[139] In this study, the administration of fomepizole, but not ethanol, quantitatively increased the renal excretion of ethylene glycol between 3–72 hours postingestion compared with control (no treatment). However, no statistical analysis was reported to verify a significant difference between the two groups. Although both ethanol and fomepizole prevented the development of renal toxicity and metabolic acidosis in this experimental setting, significant CNS depression occurred in the ethanol group, but not in the fomepizole group.

Indications

1. Patient uses

The general indications for the administration of fomepizole are similar to the indications for ethanol during ethylene glycol intoxication. The administration of fomepizole to patients with ethylene glycol poisoning is preferred to the use of ethanol in the following situations: ingestion of multiple substances with CNS depressant activity; any alteration of consciousness; the lack of intensive care beds; critically ill patient with an anion gap–metabolic acidosis of unknown etiology and potential exposure to ethylene glycol; the lack of laboratory support to monitor ethanol administration; and the presence of contraindications to the use of ethanol. Fomepizole is easier to administer, more potent, and probably causes fewer adverse reactions compared with ethanol. However, there are inadequate data to compare the efficacy and cost-effectiveness of fomepizole with ethanol. The administration of fomepizole to patients without serious complications does not require an intensive care setting as the use of ethanol does; therefore, some cost savings occur when patients are treated outside the intensive care unit. From a nursing perspective, the 12-hour dosing schedule of fomepizole is less labor-intensive compared with a continuous IV infusion or an hourly oral dosing schedule. The use of fomepizole may eliminate the need for hemodialysis if the patient presents with high ethylene glycol concentrations before the development of a serious metabolic acidosis (pH$<$7.25–7.3). There is a risk of developing hypoglycemia in children during the administration of ethanol and the use of fomepizole instead of ethanol is a theoretical advantage in young children. However, there are no data to confirm the superiority of fomepizole over ethanol in the treatment of pediatric ethylene glycol poisonings.

2. Supporting data

A multicenter study prospectively enrolled 19 patients with ethylene glycol poisoning and validated the use fomepizole in the treatment of ethylene glycol intoxication.[34] This trial demonstrated that fomepizole was an effective inhibitor of ethylene glycol metabolism that prevents the development of renal damage. In this study, all patients who had normal renal function at the time of

the loading dose of fomepizole maintained normal renal function. All patients who developed renal dysfunction and received fomepizole had high plasma concentrations of ethylene glycol and metabolic acidoses during initial presentation. A retrospective, uncontrolled, unpublished French study of 26 patients (age 19–71 years) indicated that fomepizole was safe and effective when administered either orally or intravenously as a loading dose up to 19.5 mg/kg and as a cumulative dose up to 6 g.[140] Seventeen patients received fomepizole intravenously while the remaining 9 patients received oral fomepizole, including 1 patient who received both IV and oral doses. The median serum ethylene glycol concentration on admission was 10.4 mg/dL (range 1–831 mg/dL). Consequently, the majority of these patients were not poisoned severely, with the exception of several patients seen late in their clinical course. Four of the 5 patients who required hemodialysis had renal failure. The fifth patient received hemodialysis because of the high serum ethylene glycol concentration (831 mg/dL) present on admission. All patients who developed sequelae presented to the health care facility late (17–31 hours postingestion) in the course of their intoxication.

Case reports document successful outcomes following the use of fomepizole without the use of ethanol or hemodialysis. A patient presented 12 hours after ingesting 100–200 mL antifreeze; the serum pH was 7.12. The administration of fomepizole was initiated 16 hours after ingestion and the patient recovered without sequelae.[133] Despite the rapid use of fomepizole during hemodialysis, terminal multiple-organ failure developed in a 54-year-old man, who presented 12 hours after ingestion with a plasma ethylene glycol concentration of 350 mg/dL and a pH of 6.5.[141]

Cautions

1. Contraindications

Fomepizole should not be administered to patients with known hypersensitivity reactions to fomepizole or to other pyrazole compounds.

2. Precautions

Because of venous irritation, fomepizole should not be administered as an undiluted formulation. For instruction on the dilution of fomepizole, see section on ''Administration.''

a. Drug interactions

Both ethanol and fomepizole alter the metabolism of the other. In 4 healthy male volunteers, serum ethanol concentrations of 50–150 mg/dL reduced the elimination rate of an IV dose of fomepizole 5 mg/kg by 50%.[142] The administration of fomepizole 10–20 mg/kg followed 1 hour later by ethanol 0.5–0.7 g/kg produced a 40% reduction in the elimination of the ethanol. The interaction of other inhibitors (e.g., cimetidine, ketoconazole, phenytoin) of cytochrome P_{450} with fomepizole has not been studied. Activated charcoal may adsorb fomepizole, but there are no data to estimate the extent of adsorption. Because the current formulation of fomepizole is parenteral, the use of activated charcoal does not affect the efficacy of fomepizole.

b. Pregnancy

Fomepizole is a Pregnancy Category Class C drug. Animal studies have not been conducted to assess the effect of fomepizole on reproduction. There are no data on the excretion of fomepizole in breast milk. Consequently, fomepizole should be administered to pregnant or breast-feeding women only after careful consideration of the risks and benefits, including the alternative of administering ethanol and/or hemodialysis.

c. Long-term administration

There are no studies on the carcinogenic potential of fomepizole. It is anticipated that the treatment of ethylene glycol poisoning will be short-term because there is no need to continue treatment beyond a few days.

Administration Fomepizole is available as a parenteral solution. If the Antizol solution solidifies in the vial, the solution should be warmed to liquefy the solution. Solidification does not affect the stability of Antizol. The shelf life of fomepizole vials is 2 years and the manufacturer will replace outdated vials of fomepizole free of charge. The dose of Antizol should be diluted in at least 100 mL sterile sodium chloride 0.9% or 5% dextrose solution and infused over at least 30 minutes. When refrigerated or stored at room temperature, the fomepizole in dilute solutions does not deteriorate for at least 48 hours but the use of dilute solutions of fomepizole is not recommended $>$24 hours after mixing.[140] An oral solution of fomepizole is not available in the US. Data from preclinical trials indicate that both routes of administration have comparable elimination kinetics.

Dosage The loading dose of fomepizole is 15 mg/kg, followed by 10 mg/kg every 12 hours for 4 doses by IV. After these 5 doses, the administration of fomepizole should continue at a rate of 15 mg/kg every 12 hours until the ethylene glycol concentration is undetectable or $<$20 mg/dL *and* the patient is asymptomatic with a normal arterial pH.[140] Table 5 outlines the recommended dos-

Table 5

Dosing Schedule of Fomepizole During Hemodialysis

Dose at the Beginning of Dialysis	
<6 h since last dose	Do not administer dose
>6 h since last dose	Give next scheduled dose
Dose During Dialysis	
Give dose every 4 h	
Dose at Completion of Dialysis	
<1 h since last dose	No additional dose
1–3 h since last dose	Administer ½ of next scheduled dose
>3 h since last dose	Administer next scheduled dose
Maintenance Dose Off Dialysis	
Administer next scheduled dose 12 h after last dose	

Adapted from Product Monograph Antizol, Orphan Medical, 1998.

ing schedule of fomepizole during hemodialysis. The dosing interval of fomepizole should be reduced to every 4 hours during hemodialysis. Alternately, an infusion of fomepizole 1–1.5 mg/kg/h during dialysis is sufficient to maintain therapeutic concentrations of fomepizole.[141] Monitoring of fomepizole concentrations during the treatment of ethylene glycol poisoning is not necessary. Currently, there are no specific dosing recommendations for special populations (e.g., geriatric, pediatric, hepatic, or renal dysfunction) because of the lack of clinical data.

Adverse effects During clinical trials, the most commonly *reported* adverse effects were as follows: headache (12%), nausea (11%), and dizziness (7%).[140,143] These adverse effects are mild and transient despite the attainment of concentrations 20–40 times the therapeutic (10 μM) concentration of fomepizole.[34] Less common adverse reactions include vomiting, diarrhea, abdominal pain, tachycardia, hypotension, vertigo, lightheadedness, nystagmus, slurred speech, and inebriation. Case reports have temporally associated eosinophilia, skin rash,[133] and transient (1–2 weeks), mild elevation of hepatic transaminases with the administration of fomepizole.[129] These reactions are not dose-dependent[144] and these adverse reactions were not reported in a prospective trial involving 19 patients.[34] In animal studies, pyrazole causes significant liver toxicity, but 4-methylpyrazole (fomepizole) does not cause hepatotoxicity at doses that block ethanol metabolism in the rat.[145,146] Inflammation may occur at the site of the infusion, particularly if the dose of fomepizole exceeds 25 mg/mL over 5 minutes. At a dose of fomepizole 100 mg/kg, all 3 volunteers developed a feeling of inebriation characterized by dizziness and mild difficulties with speech and vision.[143]

Extracorporeal Removal

Hemodialysis effectively removes both ethylene glycol and its toxic metabolites.[30,43] Hemoperfusion is not an effective means of removing these compounds.[147]

Clearance Rates

Hemodialysis is substantially superior to peritoneal dialysis for the removal of ethylene glycol and its toxic metabolite, glycolic acid. The serum anion gap also decreases during hemodialysis.[43] The mean clearance rate of ethylene glycol during this procedure is approximately 145–230 mL/min depending on the blood flow rate, and the elimination half-life of ethylene glycol during dialysis is 2.5–3.5 hours.[28,31,148] For example, the clearance rate of ethylene glycol was 210±3 mL/min when the blood flow was 227 mL/min during hemodialysis.[30] This value is comparable to a clearance rate of 2.2 mL/kg/min obtained during the hemodialysis of a 17-month-old infant at a blood flow rate of 50 mL/min.[149]

In a study of healthy volunteers the renal clearance of fomepizole was very low with only about 3% of a therapeutic dose excreted in the urine unchanged.[130] The renal clearance for a fomepizole dose of 10 mg/kg and 20 mg/kg was 0.022 mL/min/kg and 0.014 mL/min/kg, respectively. Case reports indicate that hemodialysis increases the clearance of fomepizole. In 2 ethylene glycol-intoxicated patients with anuric renal failure, the mean

dialysance following the administration of 10 mg fomepizole/kg and 18 mg fomepizole/kg was 117 mL/min and 137 mL/min, respectively.[127] This clearance corresponded to the removal of 50 mg fomepizole/h and 83 mg fomepizole/h, respectively.

Glycolate possesses a relatively slow elimination rate and a relatively long plasma half-life. In a series of 4 patients who received fomepizole for serious ethylene glycol intoxications, the mean plasma elimination rate for glycolate before hemodialysis was 1.08±0.67 mmol/L/h with a plasma half-life ranging up to approximately 18 hours.[45] Hemodialysis effectively removes the toxic metabolite, glycolate, and restores normal acid-base balance. Gabow and colleagues studied 3 patients who developed ethylene glycol intoxication and markedly elevated glycolic acid plasma concentrations (>7 mEq/L).[43] Hemodialysis clearance of glycolic acid was 105 mL/min and 159 mEq of glycolic acid was removed in 3 hours. After hemodialysis with a bicarbonate dialysate, the mean serum bicarbonate concentration increased from 5.5 to 20 mEq/L. In a series of 5 patients with ethylene glycol intoxication, the mean clearance of glycolate during hemodialysis was 170±23 mL/min with flow rates of 250–400 mL/min.[45] The mean plasma half-life of glycolate decreased to approximately 2.5 hours.

Indications

Hemodialysis should be considered for the following conditions: deteriorating vital signs despite intensive supportive care, significant metabolic acidosis (<7.25–7.30), and renal failure or electrolyte imbalances unresponsive to conventional therapy. A traditional indication for hemodialysis is a serum ethylene glycol concentration >50 mg/dL. Although this concentration is often used as an indication for hemodialysis, there are insufficient scientific data to determine the concentration at which renal toxicity begins. In the absence *both* of renal dysfunction *and* a significant metabolic acidosis, the use of fomepizole should obviate the need for hemodialysis, even though the serum ethylene glycol concentration exceeds 50 mg/dL.[150] If patients with high serum concentrations of ethylene glycol are not treated with hemodialysis, their acid-base balance should be monitored closely and hemodialysis instituted if a metabolic acidosis develops.

Methods

The traditional endpoint for dialysis is an undetectable serum ethylene glycol concentration **or** an EG <20 mg/dL *and* the disappearance of acid-base abnormalities and signs of systemic toxicity.[151] However, prolonged dialysis may not be necessary in a select group of patients receiving an antidote when the serum ethylene glycol concentration falls below 50 mg/dL. Case reports describe patients who recovered without sequelae following the termination of dialysis with the serum ethylene glycol concentration between 10–50 mg/dL.[94,148] These patients had normal kidney function, and no significant metabolic acidosis. Additionally, they received an ethanol infusion until the ethylene glycol concentration was undetectable. Further data are necessary to determine the exact concentration at which hemodialysis is no longer necessary for patients receiving fomepizole or ethanol. Correction of the metabolic acidosis (anion gap) and the osmol gap are adequate endpoints for dialysis, particularly when the patient is receiving fomepizole or ethanol and the serum ethylene glycol and/or glycolate concentrations are unavailable. Redistribution of ethylene glycol may result in elevation of the ethylene glycol concentrations within 12 hours after hemodialysis ceases[43] and repeat hemodialysis may be necessary. Consequently, serum osmolality and serum electrolytes should be monitored closely (every 2–4 hours) for the 12–24 hour period after hemodialysis ceases.

Increased administration of ethanol (e.g., addition of 95% ethanol to dialysate or increased infusion rates) or of fomepizole is necessary to replace the drug lost during the dialysis procedure. Administration of ethanol or fomepizole should continue after dialysis until the serum ethylene glycol concentration is nondetectable **or** <20 mg/dL *and* the patient is asymptomatic with a normal arterial pH. Hypophosphatemia is a rare complication of the prolonged dialysis of patients, who have normal serum phosphorus concentrations. Treatment of this complication includes the use of phosphorus-enriched dialysate during hemodialysis.[152]

Supportive Care

Laboratory tests for all patients who ingest potentially toxic amounts of ethylene glycol include the following: CBC, electrolytes, urinalysis, arterial blood gases, and serum osmolality as well as serum ethylene glycol and ethanol concentrations.

Cofactors

Pyridoxine and thiamine are cofactors for the metabolism of ethylene glycol.[43] Pyridoxine promotes the metabolism of glyoxylate to glycine; thiamine promotes the metabolism of glycolic acid to the nontoxic metabolite, α-hydroxy-β-ketoadipate. However, there are no clinical data to support the effectiveness of these two cofactors in

the treatment of ethylene glycol intoxication in otherwise healthy patients. Consequently, the administration of these two cofactors is necessary only in patients (e.g., alcoholics) who may have vitamin deficiencies.

Metabolic Disturbances

Magnesium is a cofactor along with thiamine pyrophosphate for the metabolism of glyoxylic acid,[153] and magnesium should be replenished, particularly in alcoholic patients. Because of concern about precipitating calcium oxalate crystals, hypocalcemia is usually not corrected unless the hypocalcemia contributes significantly to the clinical deterioration of the patient. Systemic acidosis below 7.3 can be treated with IV sodium bicarbonate solution to correct the acidosis to the normal range (7.35–7.45). Adding bicarbonate to the dialysate during hemodialysis also may restore the serum bicarbonate concentration.[43]

Fluid and Electrolyte Balance

In patients with normal renal function, IV fluids should be administered in adequate volumes to maintain urine output and the patient should be monitored carefully to detect evidence of early renal failure. The development of renal failure may require limitation of fluids in order to prevent fluid overload, and prolonged (1–4 weeks) dialysis may be necessary until normal renal function returns.

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