Treatment of Ethylene Glycol Poisoning

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Ingestion of ethylene glycol may be an important contributor in patients with metabolic acidosis of unknown cause and subsequent renal failure. Expeditious diagnosis and treatment will limit metabolic toxicity and decrease morbidity and mortality. Ethylene glycol poisoning should be suspected in an intoxicated patient with anion gap acidosis, hypocalcemia, urinary crystals, and nontoxic blood alcohol concentration. Fomepizole is a newer agent with a specific indication for the treatment of ethylene glycol poisoning. Metabolic acidosis is resolved within three hours of initiating therapy. Initiation of fomepizole therapy before the serum creatinine concentration rises can minimize renal impairment. Compared with traditional ethanol treatment, advantages of fomepizole include lack of depression of the central nervous system and hypoglycemia, and easier maintenance of effective plasma levels. (Am Fam Physician 2002;66:807-12. Copyright© 2002 American Academy of Family Physicians.)

Family physicians are often the first health care professionals to see patients with undifferentiated complaints, including patients who have acute ingestion of poison. The American Association of Poison Control Centers reported more than 4,800 and 6,000 exposures to ethylene glycol in 1997[1] and 1998,[2] respectively. Although the majority of these cases were unintentional, 21 in 1997 and 22 in 1998 were fatal. These reports are based on a surveillance system that underestimates the actual number of exposures.

Ethylene glycol is a solvent found in products ranging from antifreeze fluid and de-icing solutions to carpet and fabric cleaners.[3,4] According to results from animal studies,[4] the ingested amount of ethylene glycol required to produce toxicity in animals is approximately 1.0 to 1.5 mL per kg, or 100 mL in an adult. When treated appropriately, patients have survived much larger ingestions.[4] Ethylene glycol is an important cause of metabolic acidosis of unknown source and subsequent acute renal failure. While death and renal failure may occur with delayed diagnosis, death is uncommon in persons who receive prompt diagnosis and treatment.

Pathophysiology

Toxicity results from the depressant effects of ethylene glycol on the central nervous system (CNS). Metabolic acidosis and renal failure are caused by the conversion of ethylene glycol to noxious metabolites. Oxidative reactions convert ethylene glycol to glycoaldehyde, and then to glycolic acid, which is the major cause of metabolic acidosis.[5-7] Both of these steps promote the production of lactate from pyruvate.[4,8] The conversion of glycolic acid to glyoxylic acid proceeds slowly, further increasing the serum concentration of glycolic acid.[4] Glyoxylic acid is eventually converted to oxalic acid and glycine. Oxalic acid does not contribute to the metabolic acidosis, but it is deposited as calcium oxalate crystals in many tissues.[4]

Ethylene glycol is rapidly absorbed by the stomach and small intestine, and is quickly redistributed throughout the body. Metabolites of ethylene glycol remain in the body for several days, with calcium oxalate present in tissues for much longer.[3] The clinical syndrome of ethylene glycol intoxication has traditionally been divided into three stages: progressive involvement of the CNS, the cardiopulmonary systems, and the kidneys. However, presentation is highly variable and dependent on the amount ingested, the combined ingestion with ethanol, and the timing of medical intervention.[4]

Clinical Manifestations

Ethylene glycol produces CNS depression similar to that of ethanol. Symptoms of ethyl-

TABLE 1
Admission Laboratory Data for Illustrative Case

Component	*Value*	*Reference range in traditional units*
Sodium	141 mEq per L (141 mmol per L)	135 to 145
Potassium	3.6 mEq per L (3.6 mmol per L)	3.5 to 5.3
Chloride	106 mEq per L (106 mmol per L)	98 to 108
Glucose	103 mg per dL (5.7 mmol per L)	70 to 110
CO_2 content	6 mEq per L (6 mmol per L)	20 to 30
Anion gap	33 mEq per L (33 mmol per L)	6 to 17
BUN	8 mg per dL (2.85 mmol per L)	7 to 20
Creatinine	2 mg per dL (180 µmol per L)	0.7 to 1.3
Calcium	10.8 mg per dL (2.70 µmol per L)	8.5 to 10.4
Creatine kinase	305 U per L	35 to 230
Myoglobin	398 ng per mL	0 to 110
Osmolality	314 mOsm per kg of water	278 to 305
Arterial pH	7.30	7.35 to 7.45
$Paco_2$	13 mm Hg	34 to 38
Pao_2	136 mm Hg	65 to 75
Bicarbonate	6.21 mEq per L (6 mmol per L)	21 to 28
Blood alcohol	< 10 mg per dL	
Salicylate	< 5.0 mg per dL (0.35 mmol per L)	15 to 30

CO_2 = carbon dioxide; BUN = blood urea nitrogen; $Paco_2$ = partial pressure of carbon dioxide, arterial; Pao_2 = partial pressure of oxygen, arterial.

ene glycol toxicity include confusion, ataxia, hallucinations, slurred speech, and coma. Symptoms are most severe six to 12 hours after ingestion, when the acidic metabolites of ethylene glycol are at their maximal concentration. The presentation may be similar to ethanol intoxication, if the patient presents early or has consumed small amounts of ethylene glycol. However, an ethanol odor will be absent, and serum or respiratory ethanol levels will be too low to account for the degree of CNS depression. The absence of a strong odor of alcohol in a patient who appears intoxicated should raise the suspicion of ethylene glycol ingestion.[4]

Following a period of CNS depression, metabolic acidosis and cardiopulmonary symptoms become prominent, although coingestion of ethanol will delay the metabolic acidosis. The patient may experience nausea, vomiting, hyperventilation, and hypocalcemia with muscle tetany and seizures. Hypertension, tachycardia, and cardiac failure may ensue. Pneumonitis, pulmonary edema, and adult respiratory distress syndrome have also been reported.[3,9]

The absence of a strong odor of alcohol in a patient who appears intoxicated should raise the suspicion of ethylene glycol ingestion.

Renal involvement may become apparent within 24 to 72 hours after ingestion. Urinary crystal formation requires a sufficient amount of time for ethylene glycol to be metabolized into oxalate. Calcium oxalate formation depletes serum calcium levels and deposits in intestinal mucosa, liver, brain, heart, lung, and kidney. The excretion of calcium oxalate crystals in the urine is usually, but not always, present. Oliguric or anuric renal failure is the result in the most severe cases and, although permanent renal failure is rare, recovery of renal function may take up to two months.[3,5,9] If untreated, severe ethylene glycol toxicity is usually fatal within 24 to 36 hours.[3,5-8,10]

Illustrative Case

A 19-year-old man who presented to the emergency department was completely unresponsive. His coworkers noted that he had a decreased level of function and had stumbled and fallen several times at work. The patient eventually became alert enough to admit that he had ingested three gallons of antifreeze within the past 48 hours.

Physical examination while the patient was minimally alert but disoriented revealed a rectal temperature of 37.8°C (100.1°F); pulse, 116 beats per minute; respiration, 28 per minute; blood pressure, 152/80 mm Hg; and pulse oximetry, 98 to 99 percent saturation on room air. Neurologic examination was normal, lungs were clear to auscultation, and his extremities showed no cyanosis or edema. The patient's blood chemistry data at admission are shown in *Table 1.* Microscopic examination of the urine revealed more than 200 red

blood cells per high-power field, trace bacteria, and unidentifiable crystals. A urine toxicology screen was negative. A serum ethylene glycol level of 104 mg per dL (15.6 mmol per L) was reported from an outside laboratory approximately six and one-half hours after the blood sample was obtained.

Indicators for a quick diagnosis of ethylene glycol poisoning include hyperventilation with laboratory data suggestive of an elevated anion gap metabolic acidosis; an osmolar gap; the presence of hypocalcemia; and urinary crystals.

Diagnosis

Little correlation exists between blood levels of ethylene glycol and severity of poisoning,[4] making the diagnosis unclear at times. Therefore, clinical or laboratory evidence is an indication for treatment even if toxic levels are not demonstrated.[3,4,6,9] Indicators for a quick diagnosis of ethylene glycol poisoning include hyperventilation with laboratory data suggestive of an elevated anion gap metabolic acidosis; an osmolar gap; the presence of hypocalcemia; and urinary crystals.[4,6,8,10] Ethylene glycol or glycolic acid concentrations are definitive but may not be available[9]; in this situation, urine microscopy to identify the presence of crystals should follow determination of the anion or osmolar gaps.[4,6]

Calculation of the anion and osmolar gaps can facilitate an early diagnosis, and should be performed when the origin of metabolic acidosis is unknown. An increased anion gap with a normal chloride concentration indicates retention of nonvolatile organic acids such as glycolic acid.[5-7,9] The osmolar gap (O_g) is calculated by subtracting the calculated serum osmolality (O_c) from measured osmolality (O_m), or $O_g = O_m - O_c$ *(Table 2)*. If the serum osmolar gap is greater than 10 mOsm per kg of water, the presence of ethylene glycol poisoning is likely.[5,9] Some recent reports[6,11] suggest that a normal osmolar gap is -10 to +20 mOsm per kg of water, but current recommendations use an osmolar gap greater than 10 for initiating treatment with an antidote.[4] While elevated serum osmolality combined with an elevated anion gap strongly suggests ethylene glycol poisoning, the absence of either does not rule out a significant ingestion. If the patient presents soon after ingestion, ethylene glycol may not yet have been converted to its acid metabolites; late presentation may reveal no osmolar gap because the ethylene glycol has already been converted to toxic, but osmotically inactive, products. High serum ethanol concentrations will cause an overestimation of the osmolar gap.[9]

The serum ethylene glycol test is specific for poisoning but is not commonly available. It requires a separate, dedicated gas chromatography column. This test is expensive (approximately $90, excluding transportation and handling fees). Although the test is not a good indicator of prognosis, a documented level above 20 mg per dL (3 mmol per L) is an indication for treatment with fomepizole (Antizol).[4]

The excretion of calcium oxalate crystals in the urine is a finding in approximately one half of patients and may be accompanied by red blood cells and myoglobin casts.[5,9] Calcium

TABLE 2
Calculation of Osmolar Gap

Osmolar gap (O_g) = measured osmolality (O_m) – calculated osmolality (O_c)

$$O_c \text{ (mOsm per kg)} = 2\,[Na^+ \text{ (mEq per L)}] + \left(\frac{\text{glucose [mg per dL]}}{18}\right) + \left(\frac{\text{BUN [mg per dL]}}{2.8}\right)$$

Illustrative case:

O_m = 314 (Table 1)

$$O_c = 2\ (141 \text{ mEq per L}) + \left(\frac{103 \text{ mg per dL}}{18}\right) + \left(\frac{8 \text{ mg per dL}}{2.8}\right)$$

O_c = 282 + 5.7 + 2.9 = 290.6

O_g = 314 – 290.6 = 23.4 mOsm per kg of water

Na^+ = serum sodium level; BUN = blood urea nitrogen.

TABLE 3

AACT Criteria for Treatment of Ethylene Glycol Poisoning with an Antidote

Documented plasma ethylene glycol concentration greater than 20 mg per dL (3 mmol per L)
or
Documented recent (hours) history of ingesting toxic amounts of ethylene glycol and osmolal gap greater than 10 mOsm per kg of water
or
History or strong clinical suspicion of ethylene glycol poisoning and at least two of the following criteria:
Arterial pH less than 7.3
Serum bicarbonate level less than 20 mEq per L (20 mmol per L)
Osmolal gap greater than 10 mOsm per kg of water*
Urinary oxalate crystals present

AACT = American Academy of Clinical Toxicology.

**—Laboratory analysis by freezing point depression method only.*

Adapted with permission from Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 1999;37:538.

oxalate crystals appear in many forms, the most common being needle-shaped monohydrate. Unfortunately, the needle-shaped forms are often confused with hippurate. The dihydrate, envelope-shaped form is only present at high concentrations of calcium and oxalate, and will transform to the monohydrate. Crystalluria may develop after admission, and an initial negative microscopic result should, therefore, be repeated.[3,6,12] Examination of the urine using a Wood's lamp may be helpful, because antifreeze products contain fluorescein.[3]

Treatment

Current practice guidelines for initiating treatment of ethylene glycol poisoning have been published by the American Academy of Clinical Toxicology (AACT)[4] and are listed in *Table 3*.

Ethylene glycol is rapidly absorbed from the stomach, making treatment with gastric lavage and syrup of ipecac ineffective.[3,6] Likewise, it requires large amounts of activated charcoal to bind relatively small amounts of ethylene glycol, and the therapeutic window for this action is less than an hour.[4]

Traditional treatment of ethylene glycol poisoning consists of sodium bicarbonate, ethanol, and hemodialysis. Fomepizole is a new agent with a specific indication by the U.S. Food and Drug Administration for the treatment of ethylene glycol poisoning.[4,6,7,13,14] Ethanol and fomepizole are thought to act as inhibitors of alcohol dehydrogenase and therefore prevent the formation of acidic ethylene glycol metabolites,[4,6,7,13] but only fomepizole has demonstrated this ability.[7] If patients are diagnosed and treated with these products early in the course of poisoning, hemodialysis may be avoided. Once severe acidosis and renal failure have occurred, however, hemodialysis is necessary.

Fomepizole treatment should be initiated immediately when ethylene glycol poisoning is suspected. *Table 4*[15,16] contains specific dosing instructions for fomepizole. Within three hours of initiating therapy with fomepizole, inhibition of metabolite production and resolution of acidosis occurs, and the anion gap is normalized within four hours. If fomepizole therapy is begun before a rise in the serum creatinine concentration, damage to the kidney can be avoided.[7] When compared with ethanol, the advantages of fomepizole include a slower rate of excretion by the kidneys, lack of CNS depression or hypoglycemia, and easier maintenance of effective plasma levels.[6,7,13]

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Treatment of ethylene glycol poisoning with fomepizole, estimating an average of 3.5 doses, costs about $3,000 per patient.[7] However, cost savings from this treatment include elimination of serum ethanol measurements and fewer patients who require hemodialysis.[7,10]

Ethanol may be administered orally or intravenously. The recommended therapeutic blood ethanol level is 100 to 150 mg per dL (22 to 33 mmol per L).[4] Intravenous administration of ethanol, described in *Table 4*,[15,16] should be continued until ethylene glycol levels have been reduced below 20 mg per dL and the metabolic acidosis has been corrected. The AACT[4] provides specific dosage recommendations for ethanol in patients receiving standard treatment and patients on hemodialysis. While oral ethanol can be simply administered, it requires a conscious patient who is willing to drink the ethanol or tolerate the placement of a nasogastric tube. Advantages of intravenous infusion include greater absorption and no gastrointestinal upset. Disadvantages of treatment with ethanol include variable metabolism of ethanol; inebriation and CNS depression; frequent monitoring of serum concentrations (every one to two hours); difficulty maintaining effective serum concentrations; and the need to administer ethanol in an intensive care unit.[3,4,10]

Administration of intravenous sodium bicarbonate will correct the metabolic acidosis, increase the elimination of renal glycolic acid, and inhibit the precipitation of calcium oxalate crystals, although the latter benefit has not been proved in clinical trials.[3,12] Fifty to 100 mEq per L of intravenous fluid is usually sufficient, with a goal of maintaining a urine pH greater than 7.0.[3] If the diagnosis of ethylene glycol poisoning is not made, and the acidosis is treated only with bicarbonate, organic acids will continue to be produced.[10] Treatment with sodium bicarbonate may worsen hypocalcemia initially because of the protein binding of calcium.[5,6,8]

Hemodialysis is effective in removing ethylene glycol and glycolic acid, and correcting the metabolic acidosis.[4,5,7,8,10,13,16,17] Current indications for initiating hemodialysis are shown in *Table 5*.[4] A serum ethylene glycol concentration greater than 50 mg per dL (8 mmol per L) by itself is no longer considered a criterion for hemodialysis. In the absence of renal dysfunction and significant metabolic acidosis, the use of fomepizole should eliminate the need for hemodialysis in patients with high serum ethylene glycol concentrations; in these patients, frequent monitoring of acid-base balance is

TABLE 4
Regimens for the Treatment of Ethylene Glycol Poisoning

Fomepizole, standard treatment[15]*	
Loading dose	15 mg per kg
Maintenance dosing	10 mg per kg every 12 hours for four doses
Subsequent dosing	15 mg per kg every 12 hours†
Fomepizole during hemodialysis	
Beginning of hemodialysis:	
< 6 hours since last dose	Hold dose
≥ 6 hours since last dose	Administer next scheduled dose
During dialysis:	Administer dose every four hours
Completion of dialysis:	
< 1 hour since last dose	Hold dose
1 to 3 hours since last dose	Administer one half of next scheduled dose
> 3 hours since last dose	Administer next scheduled dose
Intravenous ethanol[16] (10 percent diluted in 5 percent dextrose)	
Loading dose	8 to 10 mL per kg, 30-minute infusion
Maintenance dose	1.4 to 2.0 mL per kg per hour

** —All doses should be administered as a slow intravenous infusion over 30 minutes. †—Fomepizole treatment is continued until ethylene glycol levels have been reduced below 20 mg per dL (3 mmol per L).*

Information from references 15 and 16.

TABLE 5
AACT Indications for Hemodialysis

Deteriorating vital signs despite intensive supportive care
Significant metabolic acidosis (pH less than 7.25 to 7.30)
Renal failure or electrolyte imbalances unresponsive to conventional therapy

AACT = American Academy of Clinical Toxicology.

Adapted with permission from Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 1999;37:555.

Compared with traditional ethanol treatment, advantages of fomepizole include a slower rate of excretion by the kidneys, lack of central nervous system depression or hypoglycemia, and easier maintenance of effective plasma levels.

necessary.[4,7] When ethanol or fomepizole is administered and renal failure is present, dialysis is the only method for removal of ethylene glycol. If metabolic acidosis persists, too little ethanol or fomepizole is being administered. Traditionally, hemodialysis is continued until ethylene glycol and glycolic acid levels cannot be detected in the blood, and there are no acid-base disturbances.[3,6]

Prolonged dialysis may not be necessary in patients treated with fomepizole or ethanol; the end point for dialysis in these patients is correction of the anion and osmolar gaps.[4] Serum osmolality levels and electrolyte levels should be monitored closely every two to four hours for 12 to 24 hours following the discontinuation of dialysis because redistribution of ethylene glycol may result in an elevated serum concentration.[4]

Pyridoxine (vitamin B_6) and thiamine (vitamin B_1) in dosages of 100 mg daily are believed to promote the conversion of intermediate byproducts into nontoxic metabolites,[3,5,6,9] but clinical data supporting their effectiveness do not exist. Therapy with 100 mg of intravenous thiamine would be appropriate if ethanol withdrawal is suspected.[4] Parenteral calcium, given as gluconate or chloride salts, may be necessary for treatment of tetany and seizures caused by hypocalcemia.[5,6,8]

The authors indicate that they do not have any conflict of interest. Sources of funding: none reported.

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