ETHYLENE GLYCOL TOXICITY

Ethylene Glycol (CH₂ OH CH₂ OH)
Ethylene glycol (EG) is a sweet tasting, clear, odorless agent found in coolant systems, de-icing solutions, automobile antifreeze and hydraulic brake fluid, as well as paints, solvents, lacquers and polish. EG alone is not toxic; instead, its four metabolites may cause severe acidosis and tissue destruction. The first case of EG toxicity was reported in 1930.¹ The 2002 Annual Report of the AAPPC showed 5,102 exposures in 2000; 27% of these exposures were in children under 19, and 88% were unintentional exposures.² Lethal toxicity may result from ingestions of 1.4 ml/kg. Because EG is highly water soluble, it is rapidly absorbed in the GI tract and distributed evenly and quickly throughout the tissues. However, there is minimal dermal or pulmonary absorption due to the low vapor pressure of the alcohol. Its volume of distribution is 0.5–0.8 L/kg and its half-life without treatment is three to eight hours. Eighty percent of EG is eliminated in the liver and the remaining 20% is excreted unchanged by the kidneys.

Toxicokinetics of Ethylene Glycol
EG is primarily metabolized by alcohol dehydrogenase (ADH) found in the liver and gastric mucosa. This enzyme metabolizes ethanol and other toxic alcohols; its inhibition prevents the metabolism of EG to its toxic metabolites. These byproducts include glycoaldehyde, glycolic acid, glyoxylic acid and oxalic acid. Glycolic acid is chiefly responsible for a large anion gap. Oxalate combines with calcium, forming crystals that deposit in the kidneys, central nervous system (CNS), gastrointestinal (GI) tract and myocardium. Resultant hypocalcemia can lead to prolonged QTc intervals and cardiac dysrhythmias in addition to persistent seizures.¹

Pathophysiology of Ethylene Glycol
The renal system is primarily affected by exposure to EG. Associated calcium oxalate crystals are deposited typically in the proximal renal tubules and may cause hydronephrosis. The direct toxicity of glycolate often results in acute tubular necrosis as well. Other organ systems are also affected after an EG ingestion. With regards to the CNS, the patient initially presents with inebriation followed by CNS depression, caused by the accumulation of glycoaldehydes, glycolate and glyoxylate. Metabolic encephalopathy results from acidosis, hypoxia and electrolyte abnormalities. Crystal deposition may also result in cerebral edema and/or seizures. Similarly, hypocalcemia caused by oxalate formation can lead to persistent seizures, as well as a prolonged QTc interval with subsequent cardiac dysrhythmias. Both metabolic acidosis and direct calcium oxalate crystal deposition can produce myocardial dysfunction. The digestive system may be affected with an initial presentation of abdominal pain and gastritis from direct irritation. As EG is metabolized, focal hemorrhages of intestinal mucosa may develop from crystal deposition.¹

There are three, classical stages of EG toxicity. The first phase, which affects the CNS, typically begins within thirty minutes and may last up to twelve hours after ingestion. Initial
symptoms include inebriation, nausea, vomiting and ataxia. CNS depression develops which leads, potentially, to coma and seizure. The second phase, which affects the cardiopulmonary system, occurs generally twelve to twenty-four hours after EG ingestion. This period typically includes tachycardia, hypertension and hyperventilation. Hypoxia can result from aspiration pneumonia and pulmonary edema, with subsequent adult respiratory distress syndrome (ARDS). The third stage, which affects the kidneys, occurs between twenty-four and seventy-two hours after EG ingestion. At this point patients develop oliguria, flank pain, acute tubular necrosis and renal failure. Cranial nerve (CN) dysfunction may occur one to two weeks after an EG ingestion. Some authors propose defining these delayed neurological sequelae as a fourth stage of toxicity while others think of it as evidence of chronic toxicity. Facial nerve paralysis (CN VII) is common; descriptions of pupillary deficits, ophthalmoplegia, hearing deficits as well as dysarthria and dysphagia are reported.3,4

Diagnosis of Ethylene Glycol Toxicity
A definitive history of an EG ingestion may not necessarily be obtained for each patient. Therefore, the diagnosis of EG poisoning should be considered when the patient presents with inebriation without the odor of ethanol, a change in mental status, crystalluria with hypocalcemia, and the combination of a large anion gap accompanied by an elevated osmolar gap.

A laboratory work up should include an EG level by gas chromatography, the gold standard of diagnosis. Other useful tests include an arterial blood gas, electrolytes, calcium, magnesium, blood urea nitrogen, creatinine, ethanol, and a lactate level. Given the volatility of alcohol, serum osmolality should be obtained by the freezing point depression method. Urinalysis should also be performed, looking for monohydrate and dihydrate crystals that either appear spindle-like or similar to the back of an envelope, respectively, on microscopic examination. Calcium oxalate crystalluria alone is not indicative of EG toxicity but when the presence of the crystals is associated with hypocalcemia, it is strongly suggestive of the diagnosis.1 Traditionally, using a Wood's lamp to check for fluorescence has been recommended. However, recent studies show that this method is not reliable.5,6

The osmol gap, obtained by subtracting the measured osmolality from the calculated osmolality, supports the diagnosis but is not definitive. A value greater than 10 mOsm/L is abnormal. Other causes of an osmol gap > 10 mOsm/L include patients with severe alcoholic/diabetic ketoacidosis, severe hyperlipidemia, chronic renal failure who have not undergone hemodialysis, as well as other toxic alcohols such as methanol, isopropyl alcohol, and glycol ethers. A normal osmol gap does not exclude toxic alcohols, either, as there is a range of -2 +/- 6 mOsm/L, and it is the change from baseline that is important.7 Multiplying the osmol gap by the conversion factor of 6.2 (based on the alcohol's molecular weight) can provide an estimation of the serum level, in units of mg/dL, while awaiting formal quantification tests.

Management of Ethylene Glycol Toxicity
As with all toxic ingestions, supportive care is the cornerstone of treatment. The patient first must be stabilized with a secure airway, adequate ventilation and circulation. Because alcohols are vasodilators, fluid resuscitation and/or vasopressors may be needed. Seizures should be controlled with benzodiazepines; calcium should be administered if hypocalcemia develops as a consequence of its binding to oxalate crystals. Decontamination could include gastric aspiration and lavage if the patient presented within one hour after ingestion. Activated charcoal is only indicated if there is suspicion of coingestants.

Antidotes for treating ethylene glycol should be started promptly. The mechanism of action of both known antidotes, ethanol and fomepizole, is competitive inhibition of alcohol dehydrogenase (ADH). The indications for antidote treatment include: 1) a documented plasma EG >20 mg/dL, or 2) a documented recent (hours) history of ingesting toxic amounts of EG and osmolar gap >10 mOsm/L, and 3) a history or strong clinical suspicion of EG poisoning and at least two of the following: arterial pH < 7.3; osmolar gap >10 mOsm/L; serum HCO3 <20 mEq/L and the presence of urinary oxalate crystals.1 Antidotes should be administered until the patient is asymptomatic with an EG level <20 mg/dL and a normal arterial pH.

Ethanol has been used as an antidote for EG poisoning since 1965, although the FDA has never approved it for this use. The loading dose of ethanol is 0.6-0.7 grams per kilogram, administered over an hour. The target blood alcohol content is 100-150 mg/dL. It may be administered intravenously or orally.
With IV administration, a 10% IV solution of ethanol is used via a central venous line. A 20% oral beverage may also be used if the IV preparation is not readily available. Four 1-oz shots of 80 proof whiskey are the 0.6g/kg ethanol loading dose for a 70 kg patient. The advantages of ethanol are that it is inexpensive and readily available. The disadvantages are that it is an unpleasant drug and it is not specific to an ICU setting, frequent blood draws and the variability of individual metabolism; many patients become agitated once inebriated. Ethanol also causes obtundation, often requiring intubation to protect the airway. Treatment with ethanol may last up to two to three days.

Fomepizole, also known as 4-methylpyrazole, 4-MP or Antizol®, is another competitive inhibitor of ADH, which was approved in December 1997 for EG poisoning in patients over twelve years old.10 It is available in a dose pack of four 1.5 ml vials containing a 1 g/ml solution. The loading dose is 15 mg/kg over thirty minutes. The maintenance dose is 10 mg/kg every twelve hours for four doses then 15 mg/kg every twelve hours. The reason for the increase in the maintenance dosage, a process known as autoinduction, is because fomepizole induces its own metabolism via the P450 mixed function oxidase system. Dosing should also be adjusted every four hours with hemodialysis. Transaminases may be elevated during treatment.10 The most frequent adverse effects include headache (14%), nausea (11%), and dizziness (7%). Treatment with fomepizole requires an average of three to four doses.

The advantages of fomepizole are much greater than those of ethanol. The ease of administration, the predictable pharmacokinetics and the tolerable, few side effects make fomepizole a more attractive antidote than ethanol. In addition, hemodialysis is less often necessary and there are fewer ICU admissions. There have also been case reports of fomepizole being well tolerated in children under twelve years old.1, 5 The major disadvantage of the drug is its cost ($1000/g). Orphan Medical, the manufacturer of fomepizole, offers free replacements of the drug if is not used within its three-year shelf life.

Hemodialysis enhances the elimination of EG and its metabolites, as well as ethanol and fomepizole. It also resolves acid-base disorders so that the anion gap is corrected. Potential indications for hemodialysis include severe metabolic acidosis (pH <7.25-7.3) unresponsive to therapy, and renal failure with an EG level > 50 mg/ dl. Exceptions are made if a patient is receiving fomepizole and is asymptomatic with a normal pH or has deteriorating vital signs and electrolyte imbalances despite supportive care.1 Several authors in the literature site examples of fomepizole obviating the need for hemodialysis, even in patients with an EG level above 50 mg/dl as long as they had normal renal function, defined as a creatinine level less than 1.5 mg/dl.11, 12

The cofactors pyridoxine and thiamine promote the formation of non-toxic metabolites. Pyridoxine is the cofactor in the conversion of glyoxylate to glycine. Thiamine promotes the conversion of glycolic acid to alpha hydroxy beta ketoacidate. Both cofactors are particularly important to administer in malnourished patients.

Conclusions

EG ingestion is a potentially lethal poisoning that, when recognized and addressed promptly, can easily be treated with an antidote. Treatment with fomepizole has many advantages over the administration of ethanol and is the only FDA approved antidote for EG toxicity. Fomepizole should be the first line agent, if available, in conjunction with hemodialysis as necessary. Due to its multiple adverse effects, ethanol should be reserved for treatment only when there is delayed access to fomepizole or it is not available. Proper storage is key to preventing all mistaken ingestions. In addition, less toxic anti-freezes made with propylene glycol instead of EG, are now available and potentially could contribute to a decreased incidence of EG poisoning.

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