Ethylene Glycol and Methanol Poisoning

Ethylene glycol is found in a number of automotive and household products, including solvents and antifreeze. It is a water soluble organic solvent with a sweet taste, which may contribute to its ingestion by children and pets. Most toxic ethylene glycol exposures result from its ingestion, acute dermal and inhalation exposure does not appear to lead to significant absorption.1 No significant corneal damage has been reported due to ocular exposure to ethylene glycol, but it may produce mild conjunctival irritation.2 In 1999, there were 136 human exposures to ethylene glycol reported to the Utah Poison Control Center. Of these, 28% were < 6 years of age. No deaths were reported to the UPCC from ethylene glycol poisoning in 1999.

Methanol (also known as “wood alcohol”) is used industrially as a solvent and is found in many commercial products such as paints, varnishes, cleaners, antifreeze, denatured alcohol and windshield wiper fluids. Like ethylene glycol, most methanol poisonings are the result of ingestion. Dermal exposure and inhalation of methanol can lead to significant absorption, but serious cases are rare.3 Ocular exposure to methanol rarely results in any symptoms greater than local irritation.2 In 1999, there were 60 human exposures to methanol reported to the UPCC. Of these, 27% were < 6 years of age. There was one death from methanol poisoning reported to the UPCC in 1999.

Toxicology

Ethylene glycol and methanol are first metabolized by alcohol dehydrogenase (ADH) (figures 1,2). The toxic effects of these compounds are primarily a result of metabolic by-products rather than the parent compound. Ethylene glycol is rapidly absorbed from the gastrointestinal tract and has an elimination half-life of 3-8 hours. The four major metabolites contribute to the development of toxicity. Metabolic acidosis occurs as a direct result of accumulation of acid metabolites and through accumulation of reduced nicotinamide-adenine dinucleotide (NADH) and inhibition of the citric acid cycle during breakdown of ethylene glycol. Oxalic acid is rapidly bound with calcium to form calcium oxalate. The deposition of the precipitated crystals in body tissue may result in tissue destruction. The metabolites of ethylene glycol are cytotoxic, especially to the renal tubules and brain.

Clinical Manifestations of Ethylene Glycol Poisoning

Phase 1 (0-12 hours)

- Initial inebriated state caused by the unmetabolized ethylene glycol
- Nausea, vomiting and hematemesis may occur
- CNS Depression: confusion, ataxia, slurred speech and depressed reflexes that may proceed to seizures and coma. The coma or stupor may persist beyond the expected elimination of the ethylene glycol and has been attributed to brain edema.

Phase 2 (12-14 hours)

- Severe anion gap metabolic acidosis
- Pulmonary edema
- Congestive heart failure
- Tachycardia and mild hypertension may be evident

Phase 3 (24 to 72 hours)

- Metabolic acidosis
- Acute oliguric or anuric renal failure (usually reversible)
- Renal failure may persist for greater than 45 days4

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Administrative (801) 581-7504  Emergency (801) 581-2151 or (800) 456-7707
Methanol is rapidly absorbed from the gastrointestinal tract and has an elimination half-life as little as 3 hours and up to 30 hours in severe overdoses.\textsuperscript{4,5} Conversion of methanol to formaldehyde in the retina is thought to be responsible for retinal edema and blindness.\textsuperscript{4} Formic acid accumulation and the production of lactic acid are responsible for the development of metabolic acidosis. Patients may initially experience inebriation as with ethylene glycol. The development of ocular toxicity and metabolic acidosis is delayed. Visual complaints have been described as “looking into a snow storm”.

\textbf{Figure 2}

<table>
<thead>
<tr>
<th>Methanol</th>
<th>Metabolism of Methanol</th>
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</thead>
<tbody>
<tr>
<td>Alcohol dehydrogenase (ADH)</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Aldehyde dehydrogenase</td>
</tr>
<tr>
<td>Formic Acid</td>
<td>Folate</td>
</tr>
<tr>
<td>$\text{CO}_2 + \text{H}_2\text{O}$</td>
<td></td>
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</tbody>
</table>

**Diagnosis**

Diagnosis of ethylene glycol and methanol poisoning can be a challenge. A history of ingestion of these substances is important, but some patients may be unwilling or unable to provide this information. Initial laboratory evaluation should include blood ethylene glycol, methanol and ethanol concentrations, electrolytes, bicarbonate, glucose, BUN, creatinine, serum osmolality (freezing point depression method) and arterial blood gases (ABG’s). Serum ethylene glycol and methanol concentrations may not be readily available, so other laboratory data may have to be relied on for diagnosis. Metabolic acidosis with a large anion gap and evidence of an osmolar gap is often seen with ethylene glycol and methanol poisoning. However, studies have shown that substantial ingestions of ethylene glycol or methanol can take place without elevating either the anion gap or the osmolar gap. Ethylene glycol or methanol poisoning is a part of the differential diagnosis for any patient presenting with metabolic acidosis.

Some antifreeze products contain fluorescein, which may cause the urine to fluoresce under a Wood’s lamp.\textsuperscript{6} A recent study demonstrated that this is not a reliable test with about a 50% accuracy and false positives in 25% of the samples.\textsuperscript{7}

**Recommended Treatment for Ethylene Glycol or Methanol Exposures**

Initial treatment of the patient who ingested ethylene glycol or methanol should include stabilization of the airway, breathing and circulation as well as other supportive care measures. Decontamination (induction of emesis, gastric lavage or the administration of activated charcoal) of the patient is generally not effective due to the rapid absorption of alcohols from the gastrointestinal tract and the poor binding to activated charcoal.

Clinical management of ethylene glycol and methanol poisoning should focus on 3 major issues:

- **Correction of metabolic acidosis**
- **Prevention of metabolism of parent compound to toxic metabolites**
- **Elimination of ethylene glycol, methanol and toxic metabolites from the body**

Metabolic acidosis should be treated with sodium bicarbonate infusion. Alkalization not only corrects metabolic acidosis, but in the case of ethylene glycol, it can prevent the formation of calcium oxalate crystals which precipitate more readily in an acidic environment. A goal for therapy should be to maintain a serum pH of at least 7.4 – 7.5.\textsuperscript{5} Calcium concentrations should be monitored in patients who have ingested ethylene glycol. Calcium supplementation may be necessary if hypocalcemia occurs as a result of the deposition of calcium oxalate crystals in the tissues.

If the patient’s ethylene glycol or methanol concentration is $> 20$ mg/dL, ADH inhibitor therapy should be initiated to block the metabolism of the parent compound to its toxic metabolites.\textsuperscript{5} Other possible indications for beginning this therapy in the absence of a documented ethylene glycol or methanol concentration include, a history of ingestion with an osmolar gap $> 10$ mOsm/L (not accounted for by other alcohols) or a history of ingestion with an anion gap metabolic acidosis.\textsuperscript{8}

**Ethanol and Fomepizole Therapy**

Ethanol is the preferred substrate for alcohol dehydrogenase. Because of its higher affinity for the alcohol dehydrogenase enzyme it is metabolized instead of ethylene glycol or methanol. This enables ethylene glycol and methanol to be eliminated from the body before being metabolized to toxic metabolites. Ethanol has no effect on the already existing toxic metabolites. When ethanol inhibits ADH, the elimination half-life of ethylene glycol is 17-18 hours and methanol is 30-52 hours (mean 40 hours).\textsuperscript{9}

Ethanol has been used for many years to treat ethylene glycol and methanol poisoning. The safety and effectiveness of this therapy is well documented. The preferred route of administration is IV, but ethanol can be given orally if IV administration is not possible.\textsuperscript{5,10} A blood ethanol concentration between 100-150 mg/dL is needed to prevent metabolism of ethylene glycol or methanol by alcohol dehydrogenase. Blood ethanol concentrations should be checked after the loading dose has been administered and hourly thereafter until a concentration between 100-150 mg/dL is achieved. Blood ethanol concentration should be checked at least three times daily after a stable concentration is achieved. As ethanol therapy may result in hypoglycemia, especially in pediatric patients, blood glucose should be also be monitored.

The Utah Poison Control Center thanks

**PEGUS Research**

for their generous contribution which allowed us to produce and distribute this newsletter.
The FDA approved fomepizole (4-MP, Antizol\textsuperscript{TM}) for the treatment of ethylene glycol poisoning in December 1997. Fomepizole is a specific antagonist of alcohol dehydrogenase. Its efficacy is similar to ethanol therapy but may have some advantage for patients who do not tolerate side effects of ethanol. Pediatric patients who are susceptible to ethanol induced hypoglycemia and CNS depression may be candidates for fomepizole therapy. Although not approved by the FDA for the treatment of methanol poisoning, fomepizole has been used successfully for this purpose.\textsuperscript{11} It would be reasonable to consider the use of fomepizole to treat methanol poisoning using the same criteria for its use in treating ethylene glycol poisoning.

No specific laboratory monitoring of fomepizole concentrations is required during treatment. Therefore, it may have some advantage in practice sites where frequent ethanol monitoring is not practical or available. An infusion pump is not required to administer fomepizole.

**Indications for Ethanol or Fomepizole Therapy**
- Serum ethylene glycol or methanol > 20 mg/dL or
- Documented recent history of ethylene glycol or methanol ingestion with increased osmolar gap > 10 mOsm/L or
- History of ethylene glycol or methanol ingestion with at least two of the following criteria:
  - Arterial pH < 7.3
  - Serum bicarbonate < 20 mEq/L.
  - Osmolar gap > 10 mOsm/L
  - Urinary oxalate crystals present

**Hemodialysis**
Hemodialysis is an effective way to remove ethylene glycol and methanol from the blood and should be considered in any patient who is symptomatic, acidicotic and has a blood ethylene glycol or methanol concentration of > 50 mg/dL.\textsuperscript{8,10} Ethanol or fomepizole therapy should begin as soon as indicated and continued during hemodialysis therapy. There is no role for peritoneal dialysis or hemoperfusion in poisoning by toxic alcohols. Some patients with normal renal function, electrolytes and acid-base status may require only ADH inhibitor treatment and not hemodialysis. If you have questions regarding the need for hemodialysis or any other treatment of an ethylene glycol or methanol poisoned patient, toxicology consultation is available through the Utah Poison Control Center.

**Other Therapies**
The adjunct use of IV thiamine and pyridoxine in ethylene glycol poisoning has also been shown to maximize the metabolism of glyoxylic acid to its non-toxic metabolites alpha-hydroxy-beta-ketoacidic acid and glycine. Folate may enhance the conversion of formic acid to CO\textsubscript{2} and H\textsubscript{2}O in methanol poisoning.

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**Dosing of IV Ethanol**
- **Loading Dose (10% Ethanol)**
  7.5 mL/kg (should be given over 20-30 minutes or longer)
- **Maintenance Dose (10% Ethanol)**
  1–2 mL/kg/h
- **Dosing during hemodialysis for 10% Ethanol**
Ethanol is removed by hemodialysis. Rate of infusion should be doubled during dialysis to maintain a therapeutic ethanol concentration.
- **Therapy should be continued until the methanol or ethylene glycol concentration is below 20 mg/dL.**

**Dosing of Fomepizole**
- **Loading Dose**
  15 mg/kg (maximum 1 g) diluted in a minimum of 100 mL of NS or D5W (given over at least 30 minutes).
- **Maintenance Dose**
  10 mg/kg every 12 hours for 4 doses or until methanol or ethylene glycol concentrations are below 20 mg/dL.
- **If More Than 4 Doses Are Required**
  Increase dose to 15 mg/kg (to offset losses due to increased metabolism of fomepizole from autoinduction)
- **Dosing during hemodialysis**
  Increase dosing interval to every 4 hours.

**Cost Comparison:** The estimated cost for the first 24 hours of treatment with fomepizole is $4,000 as compared to the cost of ethanol therapy which is approximately $100. These costs are based on average wholesale prices.

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**References**

National Poison Prevention Week is March 19–25, 2000

Please join the Utah Poison Control Center in celebrating National Poison Prevention Week by promoting awareness of unintentional poisonings among children under six years of age. Children Act Fast...so do Poisons is the general theme of National Poison Prevention Week.

Poisonings continue to be a major cause of unintentional injuries among Utah children. In 1999, there were over 40,000 reported poison exposures to the Utah Poison Control Center, 58% of these cases involved children <6 years of age.

Please call the Utah Poison Control Center at 581-7504 for a free copy of our poison awareness and prevention materials.

Public Education Materials

If you would like to provide your patients with poison prevention public education materials including: brochures, telephone stickers, emergency action cards, quarterly public newsletters and more, call for a complete list and order form. (801) 581-7504.

Utah Poison Control Center

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