Poisoning & Drug Overdose, 6e >

Chapter 68. Ethylene Glycol and Other Glycols

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Ethylene Glycol and Other Glycols

Ethylene glycol is the primary ingredient (up to 95%) in antifreeze. It sometimes is consumed intentionally as an alcohol substitute by alcoholics and is tempting to children and pets because of its sweet taste. Intoxication by ethylene glycol itself causes inebriation and mild gastritis; more importantly, its metabolic products cause metabolic acidosis, renal failure, and death. Other glycols may also produce toxicity (Table II–24).

Table II-24 Other Glycols

Compounds	Toxicity and Comments	Treatment
Diethylene glycol (DEG)	Highly nephrotoxic. Renal failure, coma, metabolic acidosis, and death have been reported after ingestion as well as repeated dermal application in patients with extensive burn injuries. Most reported incidents were from adulteration of consumer products or medications. Gastritis, hepatitis, pancreatitis, and delayed neurologic sequelae also reported after ingestion. Metabolic acidosis may be delayed longer than 12 hours after ingestion. Estimated human lethal dose is 0.05–2.0 g/kg. Calcium oxalate crystal formation documented in animals but not humans after fatal exposure. The metabolism of DEG is unclear; however, a case report documents a good outcome with fomepizole. Molecular weight is 106.	Ethanol and fomepizole may be effective. Hemodialysis indicated for patients with anuric renal failure or severe metabolic acidosis nonresponsive to medical treatments.
Dioxane (dimer of ethylene glycol)	May cause coma, liver and kidney damage. The vapor (>300 ppm) may cause mucous membrane irritation. Dermal exposure to the liquid may have a defatting action. Metabolites unknown. Molecular weight is 88.	Role of ethanol and fomepizole is unknown, but they may be effective.
Dipropylene glycol	Relatively low toxicity. Central nervous system depression, hepatic injury, and renal damage have occurred in animal studies after massive exposures. There is a human report of acute renal failure, polyneuropathy, and myopathy after an ingestion of dipropylene glycol fog solution but no reports of acidosis or lactate elevation. Molecular weight is 134.	Supportive care. There is no role for ethanol therapy.
Ethylene glycol monobutyl ether (EGBE, 2-butoxyethanol, butyl cellosolve)	Clinical toxic effects include lethargy, coma, anion gap metabolic acidosis, hyperchloremia, hypotension, respiratory depression, hemolysis, renal and hepatic dysfunction; rare disseminated intravascular coagulation (DIC), noncardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS). Oxalate crystal formation and osmolar gap elevation have been reported, but not in all cases. Serum levels in poisoning cases have ranged from 0.005 to 432	Ethanol, fomepizole, and hemodialysis may be effective.

Compounds	Toxicity and Comments	Treatment
	mg/L. Butoxyethanol is metabolized by alcohol dehydrogenase to butoxyaldehyde and butoxyacetic acid (BAA); however, the affinity of alcohol dehydrogenase for butoxyethanol is unknown. Molecular weight is 118.	
Ethylene glycol monoethyl ether (EGEE, 2-ethoxyethanol, ethyl cellosolve)	Calcium oxalate crystals have been reported in animals. Animal studies indicate that EGEE is metabolized in part to ethylene glycol; however, the affinity of alcohol dehydrogenase is higher for EGEE than for ethanol. One patient developed vertigo, unconsciousness, metabolic acidosis, renal insufficiency, hepatic damage, and neurasthesia after ingesting 40 mL. Teratogenic effect has been reported in humans and animals. Molecular weight is 90.	Ethanol and fomepizole may be effective.
Ethylene glycol monomethyl ether (EGME, 2-methoxyethanol, methyl cellosolve)	Delayed toxic effects (8 and 18 hours after ingestion) similar to those of ethylene glycol have been reported. Calcium oxalate crystals may or may not occur. Cerebral edema, hemorrhagic gastritis, and degeneration of the liver and kidneys were reported in one autopsy. Animal studies indicate that EGME is metabolized in part to ethylene glycol; however, the affinity of alcohol dehydrogenase is about the same for EGME as for ethanol. Oligospermia has been reported with chronic exposure in humans. Teratogenic effects have been reported in animals. Molecular weight is 76.	Effectiveness of ethanol and fomepizole uncertain; in one report, fomepizole did not prevent acidosis.
Polyethylene glycols	Very low toxicity. A group of compounds with molecular weights ranging from 200 to more than 4000. High-molecular-weight compounds (>500) are poorly absorbed and rapidly excreted by the kidneys. Low-molecular-weight compounds (200–400) may result in metabolic acidosis, renal failure, and hypercalcemia after massive oral ingestions or repeated dermal applications in patients with extensive burn injuries. Acute respiratory failure occurred after accidental nasogastric infusion into the	Supportive care.

Compounds	Toxicity and Comments	Treatment
	lung of a pediatric patient. Alcohol dehydrogenase metabolizes polyethylene glycols.	
Propylene glycol (PG)	Relatively low toxicity. Lactic acidosis, central nervous system depression, coma, hypoglycemia, seizures, and hemolysis have been reported rarely after massive exposures or chronic exposures in high-risk patients. Risk factors include renal insufficiency, small infants, epilepsy, burn patients with extensive dermal application of propylene glycol, and patients in alcohol withdrawal receiving ultra-high doses of IV lorazepam or diazepam. Osmolar gap, anion gap, and lactate are commonly elevated. PG levels of 6–42 mg/dL did not result in toxicity after acute infusion. A PG level of 1059 mg/dL was reported in an 8-month-old with extensive burn injuries after repeated dermal application (the child experienced cardiopulmonary arrest). A level of 400 mg/dL was measured in an epileptic patient who experienced status epilepticus, respiratory depression, elevated osmolar gap, and metabolic acidosis. Metabolites are lactate and pyruvate. Molecular weight is 76.	Supportive care, sodium bicarbonate. There is no role for ethanol therapy. Hemodialysis is effective but rarely indicated unless renal failure or severe metabolic acidosis unresponsive to medical treatment. Discontinue any drugs containing PG.
Triethylene glycol	Uncommon intoxication in humans. Coma, metabolic acidosis with elevated anion gap, osmolar gap of 7 mOsm/L reported 1–1.5 hours after ingestion of one “gulp.” Treated with ethanol and recovered by 36 hours.	Ethanol and fomepizole may be effective.

- Mechanism of toxicity
  - **Ethylene glycol** is metabolized by alcohol dehydrogenase to glycoaldehyde, which is then metabolized to glycolic, glyoxylic, and oxalic acids. These acids, along with excess lactic acid, are responsible for the anion gap metabolic acidosis. Oxalate readily precipitates with calcium to form insoluble calcium oxalate crystals. Tissue injury is caused by widespread deposition of oxalate crystals and the toxic effects of glycolic and glyoxylic acids.
  - **Pharmacokinetics.** Ethylene glycol is well absorbed. The volume of distribution is about 0.6–0.8 L/kg. It is not protein-bound. Metabolism is by alcohol dehydrogenase, with a half-life of about 3–5

hours. In the presence of ethanol or fomepizole (see below), both of which block ethylene glycol metabolism, elimination is entirely renal, with a half-life of about 17 hours.

- **Other glycols** (see Table II–24). Propylene and dipropylene glycols are of relatively lower toxicity, although metabolism of propylene glycol creates lactic acid. Polypropylene glycol and other high-molecular-weight polyethylene glycols are poorly absorbed and virtually nontoxic. However, diethylene glycol and glycol ethers produce toxic metabolites with toxicity similar to that of ethylene glycol.

II. **Toxic dose.** The approximate lethal oral dose of 95% ethylene glycol (eg, antifreeze) is 1.0–1.5 mL/kg; however, survival has been reported after an ingestion of 2 L in a patient who received treatment within 1 hour of ingestion.

III. **Clinical presentation**

- **Ethylene glycol**

  1. **During the first few hours** after acute ingestion, the victim may appear intoxicated as if by ethanol. The osmole gap (See Serum osmolality and osmole gap) is increased, but there is no initial acidosis. Gastritis with vomiting may also occur.

  2. **After a delay of 4–12 hours,** evidence of intoxication by metabolic products occurs, with anion gap acidosis, hyperventilation, convulsions, coma, cardiac conduction disturbances, and arrhythmias. Renal failure is common but usually reversible. Pulmonary edema and cerebral edema may also occur. Hypocalcemia with tetany has been reported.

- **Other glycols** (see Table II–24). Diethylene glycol and glycol ethers are extremely toxic and may produce acute renal failure and metabolic acidosis. Calcium oxalate crystals may or may not be present.

IV. **Diagnosis** of ethylene glycol poisoning usually is based on the history of antifreeze ingestion, typical symptoms, and elevation of the osmole and anion gaps. Oxalate or hippurate crystals may be present in the urine (calcium oxalate crystals may be monohydrate [cigar-shaped] or dihydrate [cuboidal]). Because many antifreeze products contain fluorescein, the urine may exhibit fluorescence under a Wood's lamp. However, false-positive and false-negative Wood's lamp results have been reported.

- **Specific levels.** Tests for ethylene glycol levels are usually available from regional commercial toxicology laboratories but are difficult to obtain quickly.

  1. Serum levels higher than 50 mg/dL usually are associated with serious intoxication, although lower levels do not rule out poisoning if the parent compound has already been metabolized (in such a case, the anion gap should be markedly elevated). Calculation of the osmole gap (See Serum osmolality and osmole gap) may be used to estimate the ethylene glycol level.

2. **False-positive ethylene glycol levels** can be caused by elevated triglycerides (see Table I–33) and by 2,3-butanediol, lactate, glycerol, and other substances when glycerol dehydrogenase is used in some enzymatic assays. An elevated ethylene glycol level should be confirmed by gas chromatography (GC).

3. Elevated concentrations of the toxic metabolite **glycolic acid** are a better measure of toxicity but are not widely available. Levels less than 10 mmol/L are not toxic. ***Note:*** Glycolic acid can produce a false-positive result for lactic acid in some assays.

4. In the absence of a serum ethylene glycol level, if the osmole and anion gaps are both normal and the patient is asymptomatic, serious ingestion is not likely to have occurred.

- **Other useful laboratory studies** include electrolytes, lactate, ethanol, glucose, BUN, creatinine, calcium, hepatic aminotransferases (ALT, AST), urinalysis (for crystals and Wood's lamp examination), measured osmolality, arterial blood gases, and ECG monitoring. Serum **beta-hydroxybutyrate** levels may help distinguish ethylene glycol poisoning from **alcoholic ketoacidosis,** which also may cause increased anion and osmole gaps. (Patients with alcoholic ketoacidosis may not have markedly positive tests for ketones, but the beta-hydroxybutyrate level will usually be elevated.)

V. Treatment

- **Emergency and supportive measures**

1. Maintain an open airway and assist ventilation if necessary (See Airway and Breathing). Administer supplemental oxygen.

2. Treat coma (See Coma and stupor), convulsions (See Seizures), cardiac arrhythmias (See QRS interval prolongation, Tachycardia, and Ventricular dysrhythmias), and metabolic acidosis (See Anion gap metabolic acidosis) if they occur. Observe the patient for several hours to monitor for development of metabolic acidosis, especially if the patient is symptomatic or there is known co-ingestion of ethanol.

3. Treat hypocalcemia with IV calcium gluconate or calcium chloride (See Calcium).

- **Specific drugs and antidotes**

1. Administer **fomepizole** (See Fomepizole (4-Methylpyrazole, 4-Mp)) or **ethanol** (See Ethanol) to saturate the enzyme alcohol dehydrogenase and prevent metabolism of ethylene glycol to its toxic metabolites. Indications for therapy include the following:

    - Ethylene glycol level is higher than 20 mg/dL.

    - History of ethylene glycol ingestion is accompanied by an osmole gap greater than 10 mOsm/L not accounted for by ethanol or other alcohols.

2. Administer **pyridoxine** (See Pyridoxine (Vitamin B_6)), **folate** (See Fomepizole (4-Methylpyrazole, 4-Mp)), and **thiamine** (See Thiamine (Thiamin, Vitamin B_1)), cofactors required for the metabolism of ethylene glycol that may alleviate toxicity by enhancing metabolism of glyoxylic acid to nontoxic metabolites.

- **Decontamination** (See Decontamination). Perform lavage (or simply aspirate gastric contents with a small, flexible tube) if the ingestion was recent (within 30–60 minutes). Activated charcoal is not likely to be of benefit because the required effective dose is large and ethylene glycol is rapidly absorbed, but it may be given if other drugs or toxins were ingested.

- **Enhanced elimination.** The volume of distribution of ethylene glycol is 0.6–0.8 L/kg, making it accessible to enhanced elimination procedures. **Hemodialysis** efficiently removes ethylene glycol and its toxic metabolites and rapidly corrects acidosis and electrolyte and fluid abnormalities.

1. **Indications for hemodialysis** include the following:

    - Suspected ethylene glycol poisoning with an osmole gap greater than 10 mOsm/L not accounted for by ethanol or other alcohols and accompanied by metabolic acidosis (pH <7.25–7.30) unresponsive to therapy.

    - Ethylene glycol intoxication accompanied by renal failure.

    - Ethylene glycol serum concentration greater than 50 mg/dL unless the patient is asymptomatic and is receiving fomepizole or ethanol therapy.

    - Severe metabolic acidosis in a patient with a history of ethylene glycol ingestion, even if the osmole gap is not elevated (late presenter).

2. **End point of treatment.** The minimum serum concentration of ethylene glycol associated with serious toxicity is not known. In addition, ethylene glycol levels are reported to rebound after dialysis ceases. Therefore, treatment with fomepizole or ethanol should be continued until the osmole and anion gaps are normalized or (if available) serum ethylene glycol and glycolic acid levels are no longer detectable.