

Fomepizole in the treatment of ethylene glycol poisoning

Tammy L. Hall, BSc Pharm

ABSTRACT

The management of ethylene glycol poisoning is reviewed, with a focus on the use of the new antidote fomepizole. Ethylene glycol is a widely used industrial agent that is also easily obtained commercially, usually as radiator antifreeze. Ingestion of as little as 30 to 60 mL can result in death or serious permanent disability. Traditional management of poisoning includes the use of ethanol, with or without hemodialysis. Activated charcoal is not indicated, and gastric lavage may be beneficial only in the first hour after ingestion. Cofactors such as pyridoxine and thiamine may be beneficial in patients deficient in these vitamins. A new antidote, fomepizole, has recently been approved for use in Canada. Like ethanol, it is a competitive inhibitor of alcohol dehydrogenase. Potential benefits of fomepizole include its ease of administration and lack of serious adverse effects. Fomepizole may be recommended over ethanol in situations in which avoidance of ethanol-induced side effects is imperative or when ethanol is not readily available. Further studies are required to verify its comparative efficacy and cost-effectiveness compared to ethanol.

Key words: adverse effects; antidotes; cofactors; cost; ethanol; ethylene glycol; fomepizole; gut decontamination; hemodialysis; levels; overdose

RÉSUMÉ

La prise en charge de l'intoxication à l'éthylène-glycol est passée en revue, l'emphase étant mise sur le recours au fomépizole, un nouvel antidote. L'éthylène-glycol est un agent industriel d'usage très répandu qu'on peut également se procurer facilement dans le commerce, généralement sous forme d'antigel pour radiateurs. L'ingestion d'aussi peu que 30 à 60 mL de cet agent peut entraîner la mort ou une incapacité grave permanente. La prise en charge traditionnelle de l'intoxication comprend le recours à l'éthanol, avec ou sans hémodialyse. Le charbon activé n'est pas indiqué et le lavage gastrique ne sera bénéfique qu'au cours de la première heure suivant l'ingestion. Les cofacteurs tels que la pyridoxine et la thiamine peuvent être bénéfiques chez des patients présentant une carence de ces vitamines. On a approuvé récemment le recours à un nouvel antidote, le fomépizole, pour usage au Canada. Comme l'éthanol, cet agent est un inhibiteur compétitif de l'alcool déshydrogénase. Les bienfaits potentiels du fomépizole comprennent sa facilité d'administration et l'absence d'effets indésirables sérieux. Le fomépizole pourrait être plus approprié que l'éthanol dans des situations où il est essentiel d'éviter des effets indésirables provoqués par l'éthanol ou lorsque celui-ci n'est pas facilement disponible. Des études plus poussées s'imposent afin de vérifier l'efficacité comparative et la rentabilité du fomépizole par rapport à l'éthanol.

Clinical Pharmacist, Emergency Medicine, Pharmacy Department, The Ottawa Hospital — Civic Campus, Ottawa, Ont.

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Introduction

Ethylene glycol is a widely used industrial agent that is also easily obtained commercially in radiator antifreeze, engine coolants, and hydraulic brake fluids.^{1,2} Ingestion of as little as 30 to 60 mL of ethylene glycol can result in death or serious permanent adverse effects.^{1,3}

Traditionally, ethanol, with or without hemodialysis, has been the mainstay of treatment for ethylene glycol overdose. Recently, fomepizole (4-methylpyrazole), another inhibitor of alcohol dehydrogenase (ADH), has been approved in Canada as an antidote in such poisonings. This article reviews the management of patients presenting with ethylene glycol poisoning, with a specific focus on the use of fomepizole.

Mechanism of toxicity

The mechanism of toxicity of ethylene glycol is primarily its conversion to toxic metabolites.^{1,3} Ethylene glycol is initially metabolized via ADH to glycoaldehyde and then glycolic acid (glycolate), which is mainly responsible for the severe metabolic acidosis seen with poisoning.³ Glycolate is further metabolized to glyoxylic acid (glyoxylate), which also undergoes metabolism via several pathways (Fig. 1). One of these gives rise to the formation of oxalic acid (oxalate), which rapidly binds to available calcium to form precipitates of calcium oxalate that are deposited in tissues and may be also found in the urine.³

Clinical manifestations

Clinically, ethylene glycol poisoning may be divided into 3 stages.³⁻⁵ The first stage involves central nervous system

(CNS) depression and occurs within 12 hours of ingestion. In this stage, the patient may experience ataxia, slurred speech and altered mental status. An anion gap metabolic acidosis and calcium oxalate crystalluria may also exist.^{3,5}

The second stage usually occurs 12 to 24 hours after ingestion and is characterized by cardiopulmonary symptoms such as hypertension, tachycardia and heart failure.^{4,5} The third stage (24–72 hours after ingestion) usually manifests as renal failure with symptoms of oliguria, flank pain and azotemia.^{3,5} Symptoms and features that indicate a poor prognosis include severe acidosis, hyperkalemia, seizures and coma.⁶

Diagnosis

The diagnosis of ethylene glycol poisoning is often difficult as many of the clinical signs and symptoms (e.g., nausea, vomiting, CNS depression) are nonspecific and may occur in many poisonings.² There are, however, certain features that should prompt the physician to consider poisoning by ethylene glycol. There is usually a distinct latent period between consumption and the appearance of distress symptoms.¹ Metabolic acidosis, as suggested by symptoms of respiratory distress such as hyperventilation, is present in most cases. This may be rapidly determined by arterial blood gas measurement.² Elevated anion and osmolar gaps also point to this type of poisoning.²

A history or suspicion of ethylene glycol intoxication should prompt investigation for the presence of an unexplained osmolal gap. This is determined by subtracting a calculated serum osmolarity ($2 [\text{Na}] + \text{glucose} + \text{urea} + \text{ethanol}$, measured in mOsm/L from a laboratory measured osmolality (determined by the freezing point depression method).³ A gap exceeding 10 mOsm/L suggests the pres-

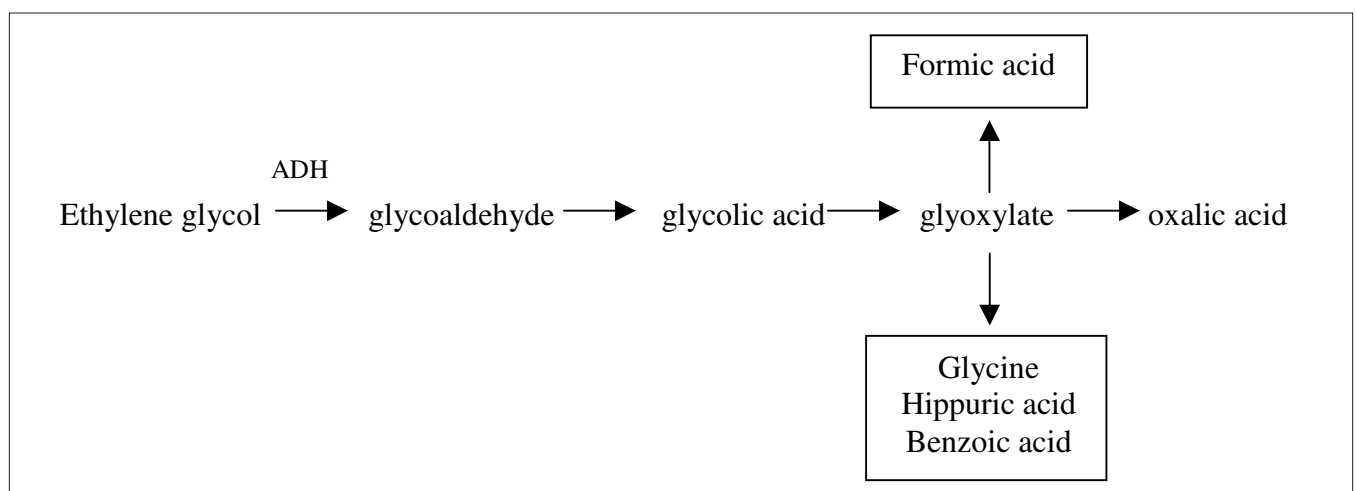


Fig. 1. Metabolic pathway of ethylene glycol

ence of small, unmeasured, osmotically active substances, such as the alcohols isopropanol, methanol or ethylene glycol. Measurement of blood concentrations of these alcohols can confirm their presence.³ However, since most institutions do not have the capacity to perform quantitative assays of ethylene glycol and methanol, treatment often is initiated on the basis of the patient's history, the presence of an elevated osmolal gap and clinical symptomatology.

There are limitations in using the osmolal gap in diagnosis. These include the following: an accurate serum osmolality may not be obtained unless the laboratory is using the freezing point depression method of measurement; the calculated serum osmolality will vary depending on which formula the clinician uses; ethylene glycol has a sufficiently large molecular weight and is such a potent toxin that it may be present at toxic levels without significantly increasing the osmolal gap; only the parent compound is osmotically active, so delayed assessment may fail to detect an osmolal gap in the presence of toxic levels of metabolites; and other causes of an increased osmolal gap may be present, such as ketoacidosis, lactic acidosis or chronic renal failure.^{2,7} Thus, an elevated osmolal gap supports a suspicion of ethylene glycol poisoning, but a normal osmolal gap does not exclude toxic ingestion.

The presence of calcium oxalate crystals in the patient's urine is highly suggestive of ethylene glycol poisoning, particularly when associated with hypocalcemia.⁴ Crystaluria may be identified through urinalysis. Urine may also be examined under a Wood's lamp (ultraviolet light) for fluorescence. Because many types of antifreeze contain sodium fluorescein as an aid for detecting radiator leaks, the urine may fluoresce under a Wood's lamp if ethylene glycol is present.^{4,5}

Finally, the most conclusive method of diagnosis is direct measurement of serum or urine ethylene glycol concentrations.² However, many institutions are not capable of readily performing such analysis. There is also often little correlation between serum levels and the severity of poisoning, since many patients are late presenting for treatment. In such cases, ethylene glycol concentrations may be low but concentrations of toxic metabolites high.²

Treatment

Gut decontamination

Activated charcoal is not indicated in the treatment of ethylene glycol poisoning because it does not adsorb significant amounts of the alcohol, but it may be useful if other drugs have been co-ingested.^{1,4} Due to rapid absorption,

gastric lavage may be beneficial only within the first hour after ingestion, before toxic symptoms develop.⁴

Hemodialysis

Ethylene glycol, as well as its metabolites, is effectively removed by hemodialysis. Indications for dialysis include deteriorating vital signs, unresponsive significant metabolic acidosis (pH less than 7.3) and renal failure or electrolyte disturbances not responsive to the usual therapy.^{3,4} A serum ethylene glycol concentration of greater than 8 mmol/L is traditionally an indication for dialysis. Hemoperfusion is not effective.⁴

Sodium bicarbonate

Metabolic acidosis should be treated aggressively with sodium bicarbonate to bring the serum pH back to within normal limits (7.35–7.45).¹ This can worsen existing hypocalcemia by increasing the protein binding of calcium. Hypocalcemia should only be treated with intravenous calcium replacement if the patient is symptomatic or experiencing persistent seizures.¹ Calcium supplementation may increase the precipitation of calcium oxalate crystals in the tissues.^{1,4}

Cofactors

Since pyridoxine and thiamine are cofactors in the metabolism of ethylene glycol to glycine and α -hydroxy- β -keto-adipic acid, supplementation may be useful in shunting the metabolism of glyoxylate and glycolic acid to these nontoxic metabolites. There is insufficient scientific data to mandate their use in ethylene glycol poisoning except in those patients who may be deficient in these vitamins (e.g., alcoholics).^{1,3,4} However, these supplements are inexpensive, safe and theoretically of benefit.

Antidotes

Indications for antidotal treatment of ethylene glycol poisoning include an ethylene glycol level of greater than 3.2 mmol/L; a documented history of recent ingestion of toxic amounts of ethylene glycol and an osmolal gap greater than 10 mOsm/L; or a history or suspicion of ethylene glycol poisoning with at least 2 of the following: arterial pH less than 7.3, serum bicarbonate less than 20 mmol/L, osmolal gap greater than 10 mOsm/L or presence of urinary oxalate crystals.⁴

Ethanol

Traditionally, ethylene glycol poisoning has been treated with ethanol, although it is not an approved antidote.⁸ Ethanol is effective because it is a substrate for ADH and

blocks the conversion of ethylene glycol to its toxic metabolites.³ It has been shown that a serum ethanol concentration of 22 to 33 mmol/L will effectively saturate ADH. This may be accomplished by giving an intravenous loading dose of 7.6 to 10 mL/kg of ethanol as a 10% v/v solution, followed by a maintenance infusion of 1 to 2 mL/kg hourly, titrated to achieve the desired serum concentrations.³ Ethanol levels are usually drawn every 1 to 2 hours during infusion to ensure maintenance within the desired range.⁸

Ethanol may also be given orally at a loading dose of 0.8 to 1 mL/kg of 95% ethanol solution, followed by a maintenance of 0.15 mL/kg hourly, diluted to a 20% solution.³ Ethanol is removed during hemodialysis, so higher doses are required if the patient is undergoing hemodialysis concomitantly.³ Also, since the major pathway for ethylene glycol metabolism is blocked, its half-life may be increased resulting in slower elimination.³ Ethanol treatment should be continued until ethylene glycol levels are undetectable and the patient is no longer acidotic.³

Fomepizole

Recently, the Canadian Health Protection Branch approved the use of fomepizole as an antidote in ethylene glycol poisoning. Like ethanol, it is a competitive inhibitor of ADH but is said to be more potent.⁸ The recommended loading dose is 15 mg/kg followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours until ethylene glycol levels are below 3.2 mmol/L.² This agent may be given intravenously or orally (only the intravenous formulation is available in Canada).

Fomepizole decreases the elimination rate of ethylene glycol during treatment. Patients with increased serum creatinine levels and renal impairment will have further prolonged ethylene glycol elimination during fomepizole therapy and will likely require hemodialysis.⁹ Fomepizole is dialyzable, and the frequency of dosing should be increased to every 4 hours during hemodialysis. Fomepizole should be given every 12 hours after the completion of dialysis until the ethylene glycol level is less than 3.2 mmol/L.² Measurement of fomepizole levels is not indicated.²

Literature review

Most of the evidence for fomepizole use in ethylene glycol poisoning is derived from case reports. Baud and colleagues described 3 patients who accidentally ingested between 100 and 300 mL of antifreeze.¹⁰ Two presented within 1 hour of ingestion and the other presented after 12 hours.

All were treated with gastric lavage. All patients had documented toxic serum levels of ethylene glycol and all received multiple, variable oral doses of fomepizole. All patients recovered without dialysis.¹⁰

Another case study by Baud and associates¹¹ described a 42-year-old man who had intentionally ingested 1.5 L of antifreeze and presented for treatment 4.5 hours later. The patient was drowsy and acidotic. Initial treatment consisted of gastric lavage, activated charcoal, sodium bicarbonate and a single loading dose of 45 g of ethanol. The ethylene glycol level was 51.6 mmol/L at 8 hours after ingestion. Fomepizole was given intravenously at 9, 21, 33, 45 and 57 hours after ingestion in doses of 9.5, 7, 3.6, 1.2 and 0.6 mg/kg, respectively. Hemodialysis was not performed, and the patient recovered with no long-term sequelae.¹¹

Harry and coworkers reported a 30-year-old man who accidentally ingested the equivalent of 100 g of ethylene glycol and was treated with fomepizole intravenously.¹² He presented 2.5 hours after ingestion. His ethylene glycol level was 56.4 mmol/L. The initial fomepizole dose given was 16.2 mg/kg at 3 hours after ingestion. Subsequent doses, given every 12 hours, were 8.1, 5.4, 2.7 and 1.35 mg/kg. Additional treatment included activated charcoal and gastric lavage. The patient made a complete recovery.¹²

The results of these case studies suggest that fomepizole may effectively treat ethylene glycol poisoning in patients with normal renal function, as none of the patients described had experienced any renal insult from ethylene glycol. However, none of the case studies used the dosing schedule currently recommended by the manufacturer.

Brent and associates conducted the only prospective clinical trial of fomepizole use in the treatment of ethylene glycol poisoning that has been published.¹³ Patients included were at least 12 years of age and had 1 of the following: a plasma ethylene glycol concentration of at least 3.2 mmol/L; 3 of the 4 following laboratory findings — an arterial pH of less than 7.3, a serum bicarbonate concentration of less than 20 mmol/L, a serum osmolar gap greater than 10 mOsm/L or oxalate crystals in the urine; or suspected ethylene glycol ingestion within the previous hour and a serum osmolar gap greater than 10 mOsm/L. Nineteen patients met the criteria for enrollment. Fomepizole was administered intravenously at a loading dose of 15 mg/kg, followed by 10 mg/kg every 12 hours for 48 hours, then 15 mg/kg every 12 hours until the plasma ethylene glycol concentration was less than 3.2 mmol/L. The mean time from ingestion to treatment was 11.4 hours. Plasma ethanol was detectable in 12 patients, with a concentration of greater than 21.7 mmol/L in 4. Seventeen of the 19 patients underwent hemodialysis in accordance with guide-

lines set out in the treatment protocol. These included: serum pH less than 7.1; a decrease of more than 0.05 in pH despite intravenous administration of sodium bicarbonate; pH less than 7.3 despite intravenous administration of sodium bicarbonate; a decrease in serum bicarbonate concentration of greater than 5 mmol/L despite bicarbonate therapy; serum creatinine greater than 265 $\mu\text{mol/L}$; increase in creatinine of 88 $\mu\text{mol/L}$ or more; or an initial ethylene glycol concentration of 8.1 mmol/L or more. Eighteen patients survived, and 1 died of cardiogenic shock. Nine patients had renal injury on presentation. The serum creatinine level in these patients increased further during treatment with fomepizole, but eventually returned to normal in 6 of these patients. No signs of renal injury developed in any person whose initial serum creatinine was within normal ranges. Also, none of the patients in whom plasma glycolate concentrations were undetectable at enrolment had measurable glycolate during treatment. It is not known how many of the patients recovered fully, as this was not one of the endpoints of the study.¹³

Flaws in this trial include its small sample size and lack of comparison with ethanol treatment. A number of patients had ingested ethanol concomitantly, which may have contributed to their successful treatment. Most patients also underwent hemodialysis, suggesting that the use of fomepizole does not necessarily eliminate the need for this procedure. In addition, the fomepizole dosing was not adjusted for hemodialysis as currently recommended by the manufacturer.² Finally, it would have been beneficial to report on the endpoint of full clinical recovery.

Adverse effects

The only adverse effects suggested as “possibly related” to fomepizole in the trial by Brent and associates were bradycardia, seizure and headache.¹³ However, the clinical course of the patients suggested that the adverse events were not due to fomepizole treatment, and similar adverse effects have not been described previously with fomepizole.¹³ The most common adverse effects reported thus far are headache, nausea and dizziness.

Other possible side effects include nystagmus, diarrhea, fever, visual problems, anemia and hypotension.² Since ethylene glycol itself can cause many of these clinical effects it is difficult to determine whether they are side effects of fomepizole therapy.

Fomepizole versus ethanol

Lack of serious adverse effects appears to be one of the

benefits of fomepizole compared with ethanol, which may often cause inebriation and hypoglycemia.^{8,14} Fomepizole also has a longer half-life, which avoids the need for a continuous infusion as with ethanol.¹⁴ There is also no need to check fomepizole levels, whereas ethanol levels require frequent monitoring.⁸ Ethanol therapy is also prone to errors in preparation and administration and may require an intensive care setting since the patient’s mental status can significantly deteriorate and lead to aspiration or require intubation.^{8,14}

The only apparent disadvantage of fomepizole is its cost (\$1000 per 1.5-g vial, average of 4 vials needed per adult patient).¹⁵ However, this may be overridden by savings in serum measurements, less labour intensive administration, and potential avoidance of intensive care unit admission.¹⁵ Pharmacoeconomic studies are needed to verify this.

Conclusions

Fomepizole is an effective treatment in ethylene glycol poisoning. It has the advantages of easier administration and fewer serious adverse effects when compared with ethanol. It has not, however, been shown to eliminate the need for hemodialysis in serious overdoses or to be more efficacious than ethanol treatment. Fomepizole may be recommended over ethanol when the patient presents with altered mental status, liver dysfunction or hypoglycemia, which would likely be exacerbated by the administration of ethanol. Fomepizole may also be used if ethanol solution is not readily available and has to be compounded, leading to a delay in treatment. Further studies are required to verify comparative efficacy and cost-effectiveness of fomepizole versus ethanol. Until then, ethanol therapy is unlikely to become obsolete.

Fomepizole was approved for use in the treatment of confirmed or suspected methanol poisonings by Health Canada’s Therapeutic Products Directorate in November 2001 (www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/noc/2001/pre2001et.txt.htm; scroll down to “Antizol Injection, 1.5mL”).

The US Federal Food and Drug Administration also recently approved fomepizole for the treatment of methanol overdose.

Competing interests: None declared.

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Correspondence to: Ms. Tammy Hall, Pharmacy Department, The Ottawa Hospital — Civic Campus, 1053 Carling Ave., Ottawa ON K1Y 4E9; 613 761-4644, fax 613 761-4350, thall@ottawahospital.on.ca

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