Treatment of patients with ethylene glycol or methanol poisoning: focus on fomepizole

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Abstract: Ethylene glycol (EG) and methanol are responsible for life-threatening poisonings. Fomepizole, a potent alcohol dehydrogenase (ADH) inhibitor, is an efficient and safe antidote that prevents or reduces toxic EG and methanol metabolism. Although no study has compared its efficacy with ethanol, fomepizole is recommended as a first-line antidote. Treatment should be started as soon as possible, based on history and initial findings including anion gap metabolic acidosis, while awaiting measurement of alcohol concentration. Administration is easy (15 mg/kg-loading dose, either intravenously or orally, independent of alcohol concentration, followed by intermittent 10 mg/kg-doses every 12 hours until alcohol concentrations are <30 mg/dL). There is no need to monitor fomepizole concentrations. Administered early, fomepizole prevents EG-related renal failure and methanol-related visual and neurological injuries. When administered prior to the onset of significant acidosis or organ injury, fomepizole may obviate the need for hemodialysis. When dialysis is indicated, 1 mg/kg/h-continuous infusion should be provided to compensate for its elimination. Side-effects are rarely serious and with a lower occurrence than ethanol. Fomepizole is contraindicated in case of allergy to pyrazoles. It is both efficacious and safe in the pediatric population, but is not recommended during pregnancy. In conclusion, fomepizole is an effective and safe first-line antidote for EG and methanol intoxications.

Keywords: ethanol, hemodialysis, metabolic acidosis

Introduction
Although relatively uncommon, ethylene glycol (EG) and methanol poisonings remain important causes of suicide and epidemic poisonings, resulting in multiple deaths and serious sequelae. In 2008, the American Association of Poison Control Centers Toxic Exposure Surveillance System reported 922 cases of EG and 825 cases of methanol exposures resulting in a total of 20 deaths. However, this undoubtedly underestimated the real number of cases. Poisonings may occur through self-harm, misuse, or potentially malicious ingestions. Toxicity of both alcohols is related to the production of toxic metabolites by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase, resulting in anion gap metabolic acidosis as well as specific organ injuries (Figure 1). Calcium oxalate, derived from EG successive oxidations, may precipitate in tissues, mainly in the renal tubules resulting in acute renal failure. Formic acid, derived from methanol oxidation, is responsible for retinal damage resulting in poorly reversible visual impairments. Recommended management includes:

- supportive care
- sodium bicarbonate to correct metabolic acidosis, to increase renal elimination of glycolate and formate, and to inhibit precipitation of calcium oxalate crystals.
• antidotes, such as a competitive ADH substrate (ethanol) or inhibitor (fomepizole) to block ADH metabolism of the toxic alcohol
• dialysis to remove the alcohol and its toxic metabolites, to correct acidosis, and, in the case of methanol poisonings, to shorten the course of hospitalization.

The objectives of this review are to examine the current recommendations regarding fomepizole in the management of toxic alcohol poisonings.

Clinical presentation and diagnosis of EG and methanol poisoning

EG is generally responsible for accidental poisonings in young children, generally due to automotive antifreeze misuse due to its bright color and sweet taste. Methanol is a component readily available in many household products such as windshield-washers, paint removers, carburetor cleaners, de-icing and embalming fluids. It is responsible for self-harm and non-intentional intoxications including in chronic alcoholics, as well as in outbreaks due to the marketing of illegal smuggled spirits. Immediately following ingestion, patients generally remain asymptomatic. Some degree of inebriation or mental status alteration may be observed in the first hours following massive ingestions. The major delayed (about 6 to 12 hours or more) effect, related to metabolic acidosis, is a hyperventilation known as Kussmaul breathing. Anion gap results from the accumulation of glycolate in EG poisoning or formate (methanol poisoning). The lactate level can easily be subtracted in a 1:1 manner from the anion gap. Measurement of EG and methanol concentrations in plasma (usually using gas chromatography) is important to confirm the diagnosis. However, these specific assays are not rapidly available in the majority of institutions. Thus, the osmol gap is used routinely as a screening test for the presence of exogenous osmotically active substances such as toxic alcohols, particularly when the ability to measure plasma concentrations of the substances is not available. The osmolal gap is the difference between the measured osmolality and the calculated osmolarity, usually within a range of 5.2 ± 7 mOsm/kg H2O. Osmolality should be measured by freezing point depression. The calculated osmolarity is obtained as follows: serum osmolality (mOsm/l) = 2xNa+ + blood urea nitrogen (mg/dL)/2.8 + glucose (mg/dL)/18. The contribution to the

![Mechanism of methanol and ethylene glycol toxicity. Symptoms are related to the toxic metabolites resulting from successive oxidations by alcohol (ADH) and aldehyde (AldDH) dehydrogenases. The primary site of metabolism is the liver although some methanol metabolism may occur within the retina.](image-url)
Management of EG and methanol poisoning

In a case of EG or methanol exposure, the patient should be immediately referred to an emergency department, a poison center, or a consultation with a medical toxicologist (Figure 2). A facility that can quickly obtain a measurement of the toxic alcohol concentration and has available antidote therapy, is preferred. Gastrointestinal decontamination with gastric lavage (unless within the first hour since ingestion), activated charcoal, or ipecac syrup is not recommended. Intentional inhalation of methanol fumes, mainly from carburetor cleaning fluid, may produce elevated plasma concentrations of methanol and formic acid, and should thus be referred, although at low risk of significant metabolic and visual complications. In contrast, in patients with EG inhalation exposures, will generally not develop systemic toxicity and can be managed out-of-hospital if asymptomatic. In EG poisoning, referral is not needed if it has been >24 hours since a potentially toxic unintentional exposure, the patient has been asymptomatic, and no alcohol was co-ingested. A witnessed taste or lick only by a child or adult who unintentionally drinks and then expectorates the product without swallowing, does not need referral.

Poisoned patients should be admitted to a medical ward and in case of life-threatening situation, to an intensive care unit. Sodium bicarbonate is required in case of severe academia (pH < 7.3). Hemodialysis, mechanical ventilation, fluids, and vasopressors may be indicated in severe poisonings. Calcium salts are only recommended in EG poisoning if hypocalcemia significantly contributes to symptoms (muscle spasms or seizures), due to the concern about precipitating calcium oxalate crystals. Other adjunctive treatments have been suggested, however with limited demonstration of benefit: pyridoxine in EG poisoning as cofactor of glycolic acid metabolism to glycine; and folic acid in methanol poisoning as cofactor of formic acid metabolism to carbon dioxide by tetrahydrofolate synthetase due to the small folate pool in humans. Because of serious morbidity and potential mortality, an antidote to block ADH metabolism of toxic alcohol should be started as soon as possible when indicated, based on history and initial physical findings while awaiting laboratory results. The absence of symptoms shortly after ingestion does not exclude a potentially toxic dose and should not be used as a triage criterion. The criteria of antidote initiation has been determined by the American Academy of Clinical Toxicology (Table 1). The decision to start the treatment cannot be solely based on the result of an assay for toxic alcohols, as this may not be readily available. The current recommendation to treat with a toxic alcohol concentration above 20 mg/dL is protective, although a higher threshold may be as safe. Prior to the availability of fomepizole, ethanol was routinely used as an antidote to treat toxic alcohol ingestion. Today, in North-American and Western-European countries, fomepizole is considered as the first-line antidote, based on its efficacy and safety. Thus, in suspected toxic alcohol ingestion or in presence of anion gap metabolic acidosis unexplained
by a corresponding increase in serum lactate concentration, we suggest the administration of a loading dose of fomepizole while awaiting definitive diagnosis.

**Fomepizole pharmacological properties**

Fomepizole (4-methylpyrazole) is a potent competitive inhibitor of ADH (>8000 times higher affinity than that of ethanol) with limited toxicity. Fomepizole interacts with ADH zinc element and coenzyme nicotinamide adenine dinucleotide, preventing its binding to the toxic alcohol.

Biochemical properties of human liver ADH as well as its role in EG and methanol metabolism have been assessed since 1964. Whilst searching in 1969 for potent ADH inhibitors, Li, Theorell and Yonetani showed that fomepizole inhibited ADH activity in human hepatocytes. In parallel, fomepizole antidotal activity was assessed in animal models by McMartin (for methanol) and Clay and Murphy (for EG). In the 1970s, Blomstrand and Theorell first administered fomepizole to human volunteers, aiming to study its consequences on ethanol biological effects. In the 1980s, Jacobsen assessed the safety of repeated doses in humans. Accordingly, fomepizole antidotal activity was assessed in animal models by McMartin (for methanol) and Clay and Murphy (for EG). In the 1970s, Blomstrand and Theorell first administered fomepizole to human volunteers, aiming to study its consequences on ethanol biological effects. In the 1980s, Jacobsen assessed the safety of repeated doses in humans. Accordingly, fomepizole has been successfully used in France in EG and methanol poisonings, since 1981. In the US, fomepizole was granted FDA marketing approval in 1997 for EG poisoning treatment, while an extension of indication was obtained in 2000 for methanol poisonings. Finally, in 1999 and 2001, two U.S. multi-center prospective clinical trials

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**Table 1 Criteria for initiating fomepizole in case of suspected EG or methanol poisoning**

- Documented recent history of ingestion of a toxic amount of toxic alcohol and osmol gap >10 mosmol/L
- Documented plasma concentration ≥20 mg/dL (3.2 mmol/L for ethylene glycol and 6.2 mmol/L for methanol)
- Suspected ingestion with at least 3 (for ethylene glycol poisoning) or 2 (for methanol poisoning) of the following criteria:
  - Arterial pH < 7.3
  - Serum bicarbonate concentration <20 mmol/L
  - Osmolal gap >10 mOsm/L
  - Oxalate crystalluria

**Notes:** Consider this criteria only for ethylene glycol exposure.
were published, definitively assessing fomepizole’s efficacy in the treatment of both toxic alcohols.29,30

Fomepizole pharmacokinetics have been extensively studied. Fomepizole’s volume of distribution is in the range of 0.6–1.0 l/kg and its plasma protein binding is low. Fomepizole has four metabolites: 4-hydroxymethylpyrazole, the only active metabolite, with approximately 1/3 the potency of the parent compound, 4-carboxypyrazole, and glucuronide conjugates of both metabolites.23,31 Fomepizole is virtually entirely eliminated by saturable hepatic metabolism, with a $K_m$ of 0.94 $\mu$mol/L, a concentration always markedly exceeded during therapeutic use.23,32,33 The currently accepted minimum effective plasma concentration, derived from studies assessing the complete inhibition of formate accumulation in methanol-poisoned monkeys, is 10 $\mu$mol/L (≈ 0.8 $\mu$g/mL).31 In the US studies, complete inhibition was reached in each case, with plasma fomepizole concentrations exceeding 10 $\mu$mol/L.31,32 Accordingly, although mostly administered by intravenous route, fomepizole is rapidly and almost completely absorbed orally, resulting in nearly identical blood levels as well as identical time above the target concentration of 10 $\mu$mol/L with both routes.32,33 Elimination is characterized by dose-dependent, non-linear zero order kinetics, with a rate of 4–15 $\mu$mol/L/h.32,34 All four metabolites are present in the urine, with a predominance of 4-carboxypyrazole.

Based on animal studies, even a single dose may induce cytochrome P450 2E1, resulting in an increase in its own elimination rate within a short time frame (after 48 hours of administration).32 However, the exact mechanism of such an autoinduction remains unclear, although a mechanism based on post-translational modifications (protein stabilization or translation) appears more possible than a transcriptional increase of the enzyme synthesis.23

When associated with ethanol, therapeutic doses of fomepizole were shown in human volunteers, to result in a 40%-reduction in the rate of elimination of ethanol. Pretreatment with fomepizole significantly prolonged ethanol neurobehavioral toxicity in a mice model.35 Conversely, ethanol was demonstrated to inhibit fomepizole metabolism, consequently increasing its blood concentration.34 Thus, previous ethanol intake or administration before fomepizole administration is allergy to pyrazole derivatives such as phenylbutazone although never associated with any of pyrazole’s serious toxicities. Case studies and clinical trials indicate that fomepizole is well tolerated, although headache (12%), nausea (11%), dizziness (7%), and injection site irritation have been reported.29,30 Other adverse reactions included rash, lymphangitis, vomiting, diarrhea, abdominal pain, tachycardia, hypotension, vertigo, slurred speech, inebriation, fever, mild transient eosinophilia and slight increases in hepatic transaminases. None of these reactions required discontinuation of therapy. However, in one reported case, fomepizole precipitated bradycardia and/or hypotension during hemodialysis.40 During pregnancy, fomepizole is still not recommended in the absence of safety data. Although not formally studied in children, several pediatric cases suggest its clinical efficacy without unusual side effects other than nystagmus.41–48

Current dosing recommendations include a 15 mg/kg loading dose followed by four 10 mg/kg doses every 12 hours during the first 48 hours and then 15 mg/kg doses every 12 hours for the remainder of the therapy.5 An increase to 15 mg/kg over 48 h was recommended by the American Academy of Clinical Toxicology, to account for a presumed enhance of fomepizole clearance due to CYP2E1 autoinduction.24,25 However, in the presence of EG or methanol, decreased fomepizole elimination was also reported, contributing to prolonging its therapeutic effects.23,34 Standard-dose regimen resulted in fomepizole concentrations considerably exceeding the minimum therapeutic concentration (>10 $\mu$mol/L).2 Therefore, a different regimen (15 mg/kg loading dose followed by 10 mg/kg each 12 hours with tapering doses until alcohol concentration is ≤30 mg/dL) is currently used in France (Table 2).9 Interestingly, other authors have suggested a higher initial 20 mg/kg dose to
Table 2 European dosage regimen of fomepizole in ethylene glycol poisoning: fomepizole is administered every 12 hours, by oral or intravenous route, according to plasma ethylene glycol concentrations

<table>
<thead>
<tr>
<th>Ethylene glycol plasma concentration (mg/dL)</th>
<th>Loading dose</th>
<th>2nd dose (T + 12 h)</th>
<th>3rd dose (T + 24 h)</th>
<th>4th dose (T + 36 h)</th>
<th>5th dose (T + 48 h)</th>
<th>6th dose (T + 60 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dL</td>
<td>mmol/L</td>
<td>2nd dose</td>
<td>3rd dose</td>
<td>4th dose</td>
<td>5th dose</td>
<td>6th dose</td>
</tr>
<tr>
<td>600</td>
<td>96</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>300</td>
<td>48</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>150</td>
<td>24</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>75</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
<td></td>
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<tr>
<td>35</td>
<td>5.6</td>
<td>15</td>
<td>7.5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–30</td>
<td>1.6–5.5</td>
<td>15</td>
<td>7.5</td>
<td>5</td>
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</tr>
</tbody>
</table>

Table 3 Pharmacokinetic parameters of ethylene glycol and methanol and their alteration in relation to fomepizole and hemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Ethylene glycol</th>
<th>Methanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethal dose</td>
<td>1.4–1.6 mL/kg</td>
<td>1.2 mL/kg (risk of blindness: 10–15 mL)</td>
</tr>
<tr>
<td>Elimination</td>
<td>Zero or 1st order</td>
<td>Zero order</td>
</tr>
<tr>
<td>Total body clearance</td>
<td>70 mL/min</td>
<td>11 mL/min</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>17–39 mL/min</td>
<td>1 mL/min</td>
</tr>
<tr>
<td>Half-life + fomepizole</td>
<td>−20 h</td>
<td>−52 h</td>
</tr>
<tr>
<td>Half-life under dialysis</td>
<td>150–210 min</td>
<td>197–219 min</td>
</tr>
<tr>
<td>Dialysis clearance</td>
<td>192–210 mL/min</td>
<td>95–176 mL/min</td>
</tr>
<tr>
<td>Metabolite clearance</td>
<td>254 mL/min</td>
<td>223 mL/min</td>
</tr>
</tbody>
</table>

Notes: *Dependent on renal function. **Dependent on blood flow during hemodialysis. **Glycolate for ethylene glycol and formate for methanol.

The place of hemodialysis when fomepizole is used

Hemodialysis is considered as an integral part of the treatment of toxic alcohol poisonings to expedite removal of the alcohol and its metabolites, thus reducing the duration of antidotal treatment. EG and methanol are efficiently cleared by dialysis (Table 3). Hemodialysis effectively clears glycolate, with an elimination half-life of 155 ± 474 min, compared to the spontaneous elimination half-life of 625 ± 474 min. In contrast, although clearing formate, hemodialysis effectiveness in significantly increasing formate elimination (half-lives: 150 ± 37 min versus 205 ± 90 min; 1.7 h versus 2.6 h; 1.80 ± 0.78 h versus 6.04 ± 3.26 h) is debated. Conflicting results are related to the small cohorts of patients while an unexpectedly great inter-individual variation of formate half-life exists.

The current criteria for hemodialysis in EG poisonings include severe metabolic acidosis, renal failure, electrolyte imbalances unresponsive to conventional therapy, and deteriorating vital signs despite intensive supportive care (Table 4). EG-poisoned patients treated with fomepizole prior to the onset of significant acidosis did not require hemodialysis. An EG concentration above 50 mg/dL (8.1 mmol/L) should no longer be considered as an independent criterion for hemodialysis in patients treated with fomepizole. Initial serum glycolic acid concentration appears to be a good indicator for hemodialysis, however, this measurement is not readily available in most hospitals. Initial glycolic acid >10 mmol/L predicts acute renal failure, with a sensitivity of 100%, a specificity of 94% and an efficiency of 98%. Dialysis is unnecessary, regardless of EG level, if glycolic acid is ≤8 mmol/L in patients receiving antidote. Anion gap >20 mmol/L or pH <7.30, but not EG concentration, are predictive of acute renal failure. In one patient with a very elevated EG concentration and despite adequate fomepizole administration, hyperosmolality and its subsequent electrolyte imbalances required hemodialysis.
Table 4 Recommendations for hemodialysis in ethylene glycol and methanol poisoning

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Arterial pH &lt; 7.10</td>
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<tr>
<td>Drop in arterial pH &gt; 0.05 resulting in a pH outside the normal range despite</td>
</tr>
<tr>
<td>bicarbonate infusion</td>
</tr>
<tr>
<td>Inability to maintain arterial pH &gt; 7.3 despite bicarbonate therapy</td>
</tr>
<tr>
<td>Decrease in bicarbonate concentration &gt; 5 mmol/L, despite bicarbonate therapy</td>
</tr>
<tr>
<td>Renal failure (serum creatinine concentration &gt; 265 μmol/L or rise in the</td>
</tr>
<tr>
<td>serum creatinine by &gt; 90 μmol/L)</td>
</tr>
<tr>
<td>Deteriorating vital signs despite intensive supportive care</td>
</tr>
<tr>
<td>Visual or neurological impairment in case of methanol poisoning</td>
</tr>
<tr>
<td>Initial plasma methanol concentration ≥ 50 mg/dL (15.6 mmol/L)</td>
</tr>
<tr>
<td>Rate of methanol decline &lt; 10 mg/dL (3.1 mmol/L) per 24 hours (delayed</td>
</tr>
<tr>
<td>hemodialysis)</td>
</tr>
</tbody>
</table>

Notes: *The recommendation for routine hemodialysis on the basis of serum         |
| concentrations alone has been called into question.*19,20,27

Methanol-induced optic nerve injury usually persists once the acute phase of toxicity has resolved.5,7

Why use fomepizole instead of ethanol?

While a comparison of fomepizole with ethanol (with or without hemodialysis) would be of interest, such a study has never been done. Interestingly, using a physiologically-based pharmacokinetic model, fomepizole was shown, if administered early enough, to be more effective than ethanol or hemodialysis in preventing EG metabolism to toxic metabolites.58

There are several reasons for preferring fomepizole: it is a more potent ADH inhibitor with a wider therapeutic index, a longer duration of action, easier dosing, and more predictable kinetics. Its administration regimen is easy, including a fixed loading dose independent of baseline alcohol concentration followed by intermittent bolus doses every 12 hours with no need for continuous infusion. Fomepizole is better tolerated, even during prolonged administration (up to 8 days), than ethanol (adjusted hazard ratio for drug event rates: 0.16 [95%-confidence interval 0.06, 0.40]).59 No significant central nervous system, hypoglycemia, liver toxicity or pancreatitis occurs with fomepizole, in contrast with ethanol therapy.60 There is no need for blood concentration monitoring, as therapeutic concentrations are reliably achieved with the proposed dosing regimens. In contrast, ethanol therapy requires blood concentration monitoring (antidote-targeting concentrations ≥ 100 mg/dL) and intravenous glucose administration, in an intensive care unit, especially for pediatric poisonings.46 Studies have shown that up to 85% of patients had ethanol concentrations above the therapeutic limit.22 While dialysis is often mandatory, adjustment of maintenance ethanol infusion rate represents an additional difficulty.

Moreover, based on a small series, we showed that asymptomatic adult patients referred to the emergency department for evaluation after ingesting a potentially toxic quantity of toxic alcohol received oral fomepizole safely and efficiently.61 Therefore we had sufficient time to obtain the plasma concentration of the alcohol, as delayed treatment may be deleterious. Given its safety, especially in patients who may subsequently be found not to be poisoned, fomepizole permits a margin of diagnostic error. Similarly, based on prehospital diagnosis using a portable blood gas analyzer, early fomepizole administration may be safely considered in the out-of-hospital setting.62 Finally, in selected EG as well as methanol patients, fomepizole may obviate the need for hemodialysis.5,9,22,27,28
There are frequent references to the minimal cost of parenteral ethanol in comparison with the relatively high cost of fomepizole ($800 per 1.5 g).\textsuperscript{3} Hospitals seeing only occasionally EG or methanol poisonings and hospitals with easily available hemodialysis,\textsuperscript{46} may prefer ethanol antidote therapy. Fomepizole shelf life (about 3 years), replacement at no charge after expiration in some cases, and limiting inappropriate use, determine the ongoing budget more than acquisition costs.\textsuperscript{6,44} To date, the costs of ethanol for intravenous use and generic fomepizole tend to be similar.\textsuperscript{5} Moreover, any comparison between both antidotes should not ignore the critical issue of laboratory costs for monitoring serum ethanol and blood glucose, the increased nursing care required for inebriated patients, and the requirement for intensive care. The risks, costs and inconvenience of prolonged hospitalization if fomepizole alone is used, must be weighed against those of hemodialysis, if ethanol is preferred. Hemodialysis represents an invasive technique with risks of adverse effects, and is not universally available, especially in cases of epidemic poisonings.\textsuperscript{3,4} Thus, we believe that ethanol combined with hemodialysis should be administered only when fomepizole is unavailable or contraindicated. However in the US, despite all these advantages, treatments with fomepizole still suffer from significant delays and is used less frequently than recommended by poison center staff.\textsuperscript{65}

Conclusion

Fomepizole is an effective and safe first-line antidote in preventing or diminishing EG and methanol toxicity. Its availability in developing countries and its optimal use in developed countries still represent important concerns. While antidotal therapy without hemodialysis is efficacious in selected cases of uncomplicated poisonings, further experience is still needed to clearly define the indications for associated hemodialysis.

Disclosure

The author reports no conflicts of interest in this work.

References


