CLINICAL THERAPEUTICS

Fomepizole for Ethylene Glycol and Methanol Poisoning

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 35-year-old man is brought to the emergency department by his wife after ingesting automobile antifreeze in an attempt at self-harm. On presentation, the patient is somnolent. He is afebrile and has a blood pressure of 126/72 mm Hg, a pulse rate of 102 beats per minute, and a respiratory rate of 24 breaths per minute. Pulse oximetry shows a hemoglobin saturation of 97% while the patient is breathing ambient air. His physical examination is normal except for tachypnea. His serum electrolyte profile and creatinine level are normal except for a serum carbon dioxide level of 17 mmol per liter. Arterial blood gas measurement reveals a pH of 7.30. Urinalysis shows microscopic hematuria and needle-shaped crystals typical of calcium oxalate. The patient's calculated serum osmolarity is 308 mOsm per liter, and his measured serum osmolality 395 mOsm per kilogram. A medical toxicologist recommends treatment with fomepizole. Subsequently, the patient's serum ethylene glycol concentration is determined to be 580 mg per deciliter (93.4 mmol per liter).

THE CLINICAL PROBLEM

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Poisoning with ethylene glycol or methanol can occur through attempted inebriation, unintentional ingestion, or intentional self-harm. In 2007, poison centers in the United States received reports of 5731 possible ethylene glycol exposures and 2283 possible methanol exposures.[1] Because reporting of such exposures is not mandatory, these data undoubtedly underestimate the total number of cases.

Ethylene glycol is a component of antifreeze, which is the major source of exposure in poisonings. Antifreeze generally has a bright color, and its ethylene glycol content confers a sweet taste. These qualities render it a common source of pediatric ingestions. The principal clinical features of ethylene glycol poisoning are some degree of inebriation or alteration in consciousness, a profound metabolic acidosis, oxalate crystalluria, and acute renal failure. In severe cases, clinical hypocalcemia, multiorgan-system failure, and death occur.[2] There are no data on the rate of death among persons with untreated ethylene glycol poisoning.

Methanol poisoning most often occurs from the ingestion of windshield-washer fluid. Methanol is also used in copy machines and as an ingredient in canned-heating products, embalming fluids, and paint removers. Methanol poisoning is a well-known consequence of ingesting "moonshine" liquor.[3] The ingestion of small quantities of methanol induces a profound metabolic acidosis, visual changes that may progress to blindness, and (in severe cases) multiorgan-system failure and death.[4] Untreated methanol poisoning is associated with a rate of death of 28% and a rate of visual deficits or blindness of 30% in survivors.[3]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Although there is little toxicity associated with ethylene glycol itself, it is metabolized by successive oxidations to active metabolites (Fig. 1A). One of these metabolites is oxalic acid, which may combine with ionized calcium in plasma to form calcium oxalate. Calcium oxalate precipitates in the renal tubules and is thought to be the cause of ethylene glycol–induced renal injury,[5,6] although some studies suggest a role for other metabolites.[7] The prominent metabolic acidosis is due to circulating glycolic acid.[8-10]

Like ethylene glycol, methanol itself is not responsible for the major adverse effects of its ingestion. Rather, it is metabolized to formaldehyde, which is subsequently oxidized to formic acid (Fig. 1B). Formic acid is the cause of the retinal and optic-nerve damage seen in patients who survive serious methanol poisoning.[11,12] Although the primary site of metabolism of methanol is the liver, some metabolism appears to occur in the retina as well, and local retinal conversion to for-

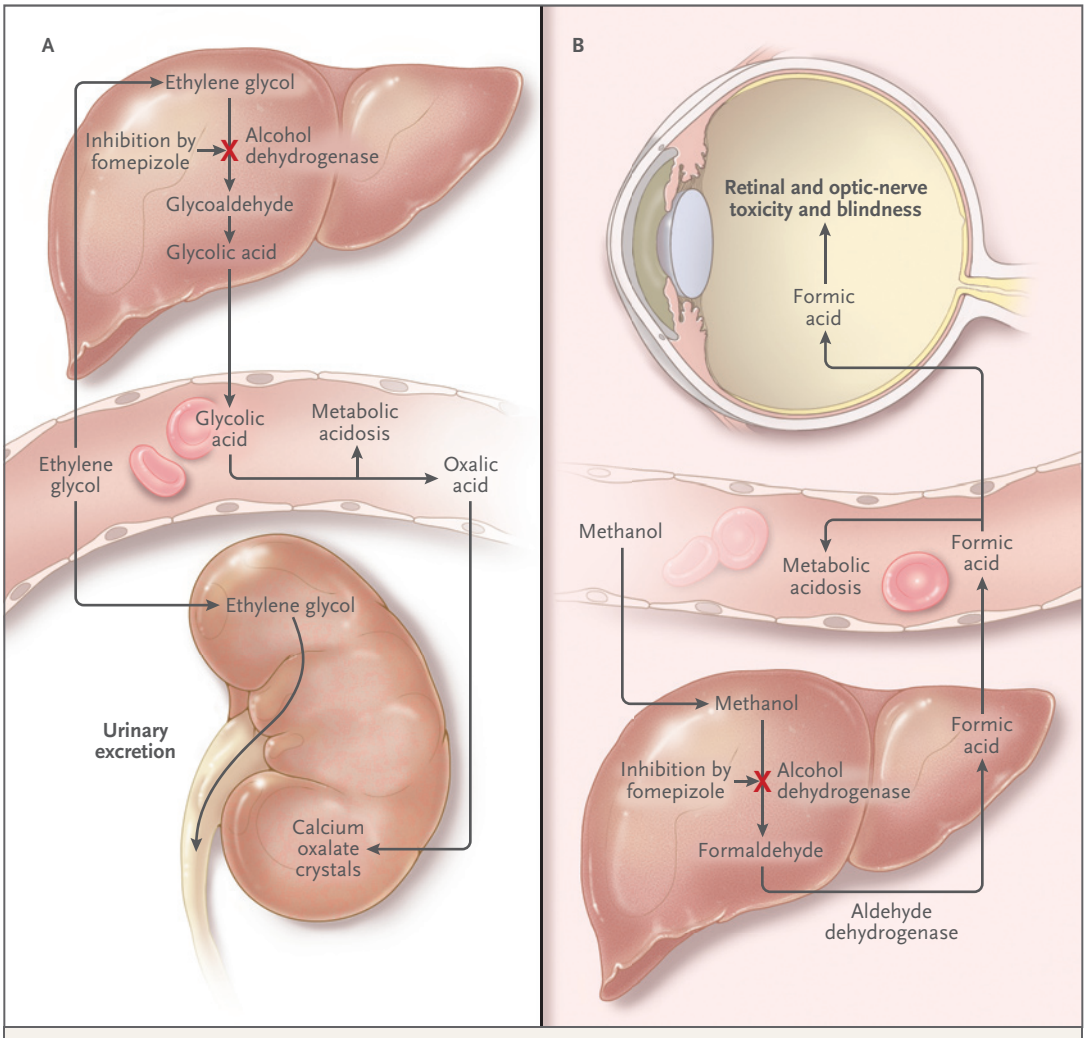

Figure 1. Effect of Fomepizole on the Pathophysiological Effects of Poisoning from Ethylene Glycol and Methanol.

Panel A shows the metabolic transformation of ethylene glycol to glycolic acid, which is responsible for metabolic acidosis. Glycolic acid is further metabolized through the intermediate glyoxylic acid to oxalic acid. When the solubility product of calcium oxalate is exceeded, precipitates form in the renal tubules, causing acute kidney injury. In severe cases, calcium oxalate crystals deposit diffusely in multiple organs. Panel B shows similar effects of fomepizole on methanol metabolism.

mic acid may be a factor in the retinal toxicity of methanol.[13,14]

The metabolism of both ethylene glycol and methanol occurs primarily through the hepatic enzyme alcohol dehydrogenase (Fig. 1A). Ethanol, which is a competitive substrate for alcohol dehydrogenase, can be administered to inhibit the metabolism of ethylene glycol or methanol, followed by hemodialysis to remove both the parent compound and its metabolites.[15-17] However, ethanol has erratic pharmacokinetics[18-20] and can cause changes in mental status,[20] hypoglycemia,[18,19] and pancreatitis.[19]

Fomepizole (4-methylpyrazole) is a competitive inhibitor of alcohol dehydrogenase that prevents the formation of metabolites of ethylene glycol[8] and methanol.[21] It is most effective when given early, before significant quantities of metabolites are formed. Given the efficacy of inhibition of alcohol dehydrogenase by fomepizole,[8,21,22] the prognosis is primarily dependent on the time from ingestion to the initiation of therapy and the amount of the toxic metabolite that has accumulated, rather than the plasma concentration of the parent compound at the time that fomepizole is administered.[8,21] Fomepizole was approved in the United States for the treatment of ethylene glycol poisoning in 1997; in 2000, an indication for methanol toxicity was added.

CLINICAL EVIDENCE

The primary evidence for the efficacy of fomepizole in the treatment of human poisonings derives from two retrospective case series,[23,24] another case series related to an outbreak of methanol toxicity in Norway,[25,26] and two prospective clinical trials.[8,21] None of the studies involving humans used untreated control subjects or compared fomepizole with ethanol therapy.

The two prospective clinical studies were substudies of the Methylpyrazole for Toxic Alcohols (META) trial.[8,21] These studies used formal assessment and treatment protocols and specific diagnostic criteria. Because of the lack of experience with fomepizole at the time of the META trial, patients underwent hemodialysis if their plasma concentration of ethylene glycol or methanol exceeded 50 mg per deciliter (8.1 mmol of ethylene glycol per liter; 15.6 mmol of methanol per liter) or if they had prespecified signs of severe poisoning.

The ethylene glycol substudy[8] of the META trial enrolled 23 consecutive patients, 19 of whom ultimately met the criteria for ethylene glycol poisoning. Eighteen patients survived; the one death occurred in a patient with severe acidemia whose clinical course was complicated by a myocardial infarction immediately before presentation and who died of cardiogenic shock on the day of admission. All 10 patients who had normal renal function at the time of presentation showed no subsequent kidney injury despite plasma ethylene glycol concentrations as high as 446 mg per deciliter (71.9 mmol per liter) and arterial pH levels as low as 7.16. These patients all had plasma glycolic acid concentrations of under 80 mg per deciliter (10.5 mmol per liter).[8]

The META trial also studied methanol poisoning in 11 consecutive patients,[21] of whom 2 died. Both of the deaths occurred in patients who were comatose with signs of anoxic brain injury on admission, who had severe acidemia (pH levels of 6.90 and 7.01), and who had plasma formic acid concentrations of 198 and 129 mg per deciliter (43 and 28 mmol per liter), respectively. The remaining nine patients survived even though several of them were initially comatose with pH levels as low as 6.90, plasma methanol concentrations as high as 612 mg per deciliter (191.0 mmol per liter), and visual deficits severe enough that they were only able to count fingers. All these patients regained their baseline visual acuity. In contrast to the two patients who died, all survivors had plasma formic acid concentrations of no more than 100 mg per deciliter (21.7 mmol per liter).

CLINICAL USE

In all cases of suspected ethylene glycol or methanol poisoning, immediate consultation with a medical toxicologist or a poison control center is strongly recommended. These poisonings constitute a potentially serious medical emergency, and the guidance of an experienced specialist may prove decisive in the treatment of such patients.

Either ethanol or fomepizole may be used to inhibit alcohol dehydrogenase. However, fomepizole has superseded ethanol as the antidote of choice in most settings in the United States. There are no contraindications to the use of fomepizole except in the case of previous allergic reaction, none of which have been reported.

On the basis of the META study, traditional practice guidelines indicate that treatment of toxic alcohol poisoning can be based on a measured blood concentration of the suspected agent (Table 1).[17,27] However, the decision to start therapy must be made expeditiously, and results of assays for toxic alcohols are usually not available promptly enough to assist in this decision. Alternative criteria, according to the guidelines, include a documented recent ingestion of a toxic alcohol and metabolic evidence consistent with toxic alcohol poisoning.[17,27] However, with the introduction of fomepizole, it has become increasingly evident that these criteria are also probably too stringent. Many experts consider a suspicion of ingestion or the presence of a metabolic acidemia of unknown cause to be sufficient to start therapy.

Fomepizole is given intravenously; recommended doses are listed in Table 2. The plasma fomepizole concentration that is required to inhibit alcohol dehydrogenase is approximately 0.8 μg per milliliter (10 μmol per liter),[28,29] and clinical trials[8,21] have shown that levels in this range are obtained during therapy. For patients undergoing dialysis, the interval between doses is shortened. Repeated administration of fomepizole has been reported to induce cytochrome P-450 metabolism.[30] Therefore, current guidelines recommend an increased dose for patients who require more than 48 hours of treatment[17,27] (Table 2). No dose adjustments are necessary for patients with renal or hepatic disease, and no significant interactions with other medications have been reported.

Patients with ethylene glycol or methanol poisoning are often treated in intensive care units. Intubation and ventilatory support may be required in severely intoxicated patients, as may hemodynamic support with fluid resuscitation and vasopressors. For patients with severe acidemia (a pH level below 7.3), the administration of sodium bicarbonate is recommended. However, less severely poisoned patients may be treated on general medical wards or in medical psychiatric units.

Hemodialysis is an important adjunctive therapy in patients who are treated with ethanol for toxic alcohol poisoning. The existing clinical guidelines,[17,27] which are based more on clinical experience than on research data, recommend considering hemodialysis for any ethanol-treated patient with a serum concentration of ethylene glycol or methanol of at least 50 mg per deciliter (8.1 mmol of ethylene glycol per liter; 15.6 mmol of methanol per liter), significant acidemia, a major decrement in renal function (for ethylene glycol poisoning), or visual signs or symptoms (for methanol poisoning).

The introduction of fomepizole has obviated the need for hemodialysis in many patients, especially if they do not have signs of renal or optic injury and do not have profound acidemia.[23,26,31] Patients with blood methanol concentrations as high as 146 mg per deciliter (45.6 mmol per liter) have been treated with fomepizole alone without sequelae.[24] In my institution, patients with a blood ethylene glycol concentration of more than 700 mg per deciliter (112.8 mmol per liter) have been treated with fomepizole alone without adverse effects or sequelae.

In patients with ethylene glycol poisoning, the administration of pyridoxine has been frequently advocated as an adjunctive therapy, because pyridoxine is a cofactor in the metabolism of gly-

Table 1. Criteria for the Initiation of Therapy in Patients with Known or Suspected Ethylene Glycol or Methanol Poisoning.*

Ethylene glycol
Documented plasma concentration of ethylene glycol of ≥20 mg per deciliter (3.2 mmol per liter)
Or
Documented recent history of ingestion of toxic amounts of ethylene glycol and an osmolal gap of >10 mOsm per liter
Or
Suspected ethylene glycol ingestion and at least three of the following criteria:
Arterial pH level of <7.3
Serum carbon dioxide level of <20 mmol per liter
Osmolal gap of >10 mOsm per liter
Oxalate crystalluria
Methanol
Documented plasma methanol concentration of ≥20 mg per deciliter (6.2 mmol per liter)
Or
Documented recent history of ingestion of toxic amounts of methanol and an osmolal gap of >10 mOsm per liter
Or
Suspected methanol ingestion and at least two of the following criteria:
Arterial pH level of <7.3
Serum carbon dioxide level of <20 mmol per liter
Osmolal gap of >10 mOsm per liter

* Data are from Barceloux et al.[17] and the American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning.[27]

Table 2. Recommended Doses of Fomepizole for Ethylene Glycol or Methanol Poisoning.*

For patients not undergoing hemodialysis
Loading dose: 15 mg per kilogram of body weight, followed by 10 mg per kilogram every 12 hr; after 48 hr, 15 mg per kilogram every 12 hr
For patients undergoing hemodialysis
Same doses administered to patients who are not undergoing hemodialysis, except that the drug is given 6 hr after the first dose and every 4 hr thereafter

* All doses are administered intravenously over a 30-minute period. These regimens have been shown to maintain therapeutic plasma fomepizole concentrations both in patients undergoing dialysis and in those not undergoing dialysis.[8,21]

colic acid to glycine.[18] However, there are sparse data supporting any beneficial effect of such treatment.

In patients with methanol poisoning, the administration of folate is of theoretical benefit, because formic acid is catabolized to carbon dioxide and water by tetrahydrofolate synthetase, an enzyme that is dependent on stored folate.[32] An initial intravenous dose of 1 mg per kilogram of body weight (up to 50 mg) of folinic acid (leucovorin), the activated form of folate, is typically given. Stereospecific levoleucovorin has become available.[33] If used, it should be administered at one half the dose of leucovorin. Subsequently, folic acid may be administered at the same dose as leucovorin every 6 hours until the metabolic acidosis resolves.

Patients with ethylene glycol poisoning who have signs of renal injury should be followed with daily measurements of serum creatinine until their renal function returns to baseline. Those who have severe kidney injury should be treated in a standard fashion, including hemodialysis, if necessary. The typical clinical picture is one of acute and transient renal failure. There is no evidence of the development of latent renal injury that may be manifested after the initial episode has resolved.

The visual deficits from methanol poisoning are most often reversible if they are treated early with fomepizole.[21,24,34,35] However, for patients presenting late, optic injury may be permanent. Once the diagnosis of methanol poisoning is made, visual function should be followed during the acute phase by daily assessment of visual acuity and color perception. There is no specific treatment for methanol-induced optic-nerve injury that persists once the acute phase of the toxicity has resolved.

Clinical guidelines,[17,27] which are based on clinical experience rather than evidence, call for continuation of treatment until the plasma ethylene glycol or methanol concentration is below 20 mg per deciliter (3.2 mmol of ethylene glycol per liter; 6.2 mmol of methanol per liter). The time that is required to eliminate a fomepizole dose of 10 mg per kilogram is approximately 24 hours.[36] In addition, most patients who receive the standard-dose regimen have fomepizole plasma levels that considerably exceed the minimum therapeutic concentration.[8,21] For these reasons, fomepizole can be safely stopped before the plasma level of ethylene glycol or methanol reaches the traditional threshold. Although the exact point at which treatment can be terminated has not been defined, it is undoubtedly safe to discontinue therapy when the plasma ethylene glycol or methanol concentration is 30 mg per deciliter (4.8 mmol of ethylene glycol per liter; 9.4 mmol of methanol per liter).

Fomepizole has recently attained generic-drug status. The current cost of fomepizole is approximately $800 per 1.5 g, or $373 to $533 per dose. In the META trials, patients with ethylene glycol poisoning received a median of 3.5 doses (range, 1 to 7),[8] and those with methanol poisoning received a median of 4 doses (range, 1 to 10).[21]

ADVERSE EFFECTS

Because ethylene glycol and methanol poisoning occur relatively infrequently, most trials and clinical series reporting the effects of fomepizole therapy are small. In addition, the agent is used only for a short time and in patients who are acutely ill. As a result, it is difficult to estimate the incidence of adverse effects of fomepizole. The most common adverse effect is burning at the infusion site. Other reported effects include headache, nausea, dizziness, agitation, eosinophilia, and seizures.[8,21,24,37] It is unknown whether these effects were due to fomepizole treatment or the patients' poisonings.

In a study of 15 human volunteers given fomepizole for up to 5 days, increases in levels of alanine aminotransferase, aspartate aminotransferase, or both were seen in 6 subjects. The peak reported value for alanine aminotransferase was 109 U per liter, 2.5 times the upper limit of the normal range. This effect was transient, did not appear to be of any clinical significance, and was not dose-related.[38] Increased aminotransferase

levels have been rarely reported during therapeutic use of fomepizole as well.[39] These increases tended to resolve despite continued treatment. There were no reports of fever, eosinophilia, or rash in this study.

AREAS OF UNCERTAINTY

As noted above, the appropriate threshold concentration of ethylene glycol or methanol at which an alcohol dehydrogenase inhibitor should be started has not been established. The currently recommended value[17,27] of 20 mg per deciliter is undoubtedly protective, since there have been no reports of harm to patients with the use of this criterion. However, it is plausible that a higher treatment threshold may be equivalently safe. The advice of a medical toxicologist should be sought in making the decision to initiate or withhold treatment.

When patients with ethylene glycol or methanol poisoning present many hours after ingestion, a significant proportion of the parent compound has already been metabolized to glycolic and oxalic acid or to formic acid, respectively (Fig. 1). These metabolites, as well as the parent alcohol, can be efficiently cleared by hemodialysis.[9,15,16,26,40] However, it is unknown whether hemodialysis, once alcohol dehydrogenase has been efficiently inhibited, affects the outcome in such patients.

When fomepizole is not available, ethanol (combined with hemodialysis) remains the most appropriate alternative for treatment of ethylene glycol or methanol poisoning. Whether ethanol is a reasonable alternative for some patients even when fomepizole is available is debatable,[41,42] but in practice the use of fomepizole has increasingly become the preferred treatment, at least in the United States. The costs of ethanol for intravenous use and generic fomepizole are similar.

Although treatment with fomepizole clearly eliminates the need for hemodialysis in many cases of ethylene glycol poisoning, this is not always clear with methanol poisoning. In one small study, the mean elimination half-time of methanol when alcohol dehydrogenase was inhibited was 52 hours.[25] This finding argues for comparatively more frequent use of hemodialysis in patients with methanol poisoning. The practical threshold for hemodialysis in such patients has not been determined.

The pediatric experience with fomepizole is strictly anecdotal. However, on the basis of the few available reports in this population, the use of the drug appears to be both efficacious and without unusual adverse effects.[20,43-48] There are no data regarding the use of fomepizole during pregnancy.

GUIDELINES

The American Academy of Clinical Toxicology has promulgated practice guidelines for the treatment of ethylene glycol[17] or methanol[27] poisoning. These guidelines call for fomepizole to be the first-line agent in the treatment of both types of poisoning, with ethanol to be used if fomepizole is unavailable. The guidelines list recommended doses of fomepizole that are similar to those described in this review (Table 2).

RECOMMENDATIONS

The patient in the vignette presents with mild metabolic acidemia after ingestion of ethylene glycol. This information alone is sufficient to initiate fomepizole therapy. Thus, as a consulting medical toxicologist, I would agree with the recommendation to begin fomepizole therapy imme-

Table 3. Methods for Determining the Osmolal Gap and Its Application in Screening for Ethylene Glycol or Methanol Poisoning.

Calculation of the osmolal gap
Osmolal gap = measured serum osmolality − calculated serum osmolarity
Calculation of serum osmolarity (traditional units)
Serum osmolarity = ([2 × sodium] + [BUN ÷ 2.8] + [glucose ÷ 18.1])*
Application of the osmolal gap to patient in vignette
Osmolal gap = 395 mOsm/kg − 308 mOsm/liter = 87†
Thus, 87 mOsm/liter are unaccounted for, so if the contribution of ethylene glycol to the osmolal gap is: ethylene glycol (mg/dl) ÷ 6.2, the value for ethylene glycol is 6.2 × 87 = 539 mg/dl

* In this equation, serum sodium is given in millimoles per liter, and levels of blood urea nitrogen (BUN) and glucose are given in milligrams per deciliter. If ethanol, ethylene glycol, or methanol is present, its contribution to the osmolal gap is as follows (all expressed in milligrams per deciliter): ethanol ÷ 4.6, ethylene glycol ÷ 6.2, and methanol ÷ 3.2. The same equation using international units is: serum osmolarity = ([2 × sodium] + BUN + glucose), in which serum sodium is measured in millimoles per liter, and glucose and BUN are measured in millimoles per liter of serum. If ethanol, ethylene glycol, or methanol is present, its contribution to the osmolal gap is measured in millimoles per liter.

† It is conventional to compare the calculated serum osmolarity (in milliosmoles per liter) with the measured serum osmolality (in milliosmoles per kilogram), despite the fact that the units of measure are not the same. Because the specific gravity of human serum is 1.01, one liter of serum weighs approximately 1 kg. Therefore, the osmolarity and osmolality of serum are approximately the same.

diately, without waiting for the result of a measured ethylene glycol concentration. The patient's osmolal gap can be calculated from the data that are provided, suggesting an ethylene glycol concentration of approximately 539 mg per deciliter (86.8 mmol per liter) (Table 3).[49]

If treatment is initiated while the patient's renal function is normal, his prognosis is excellent. His hemodynamic status and respiratory function should be carefully monitored, but if his vital signs remain stable, he could be treated on a general medical ward and would not require admission to an intensive care unit. Given his attempt at self-harm, a psychiatric evaluation and close observation are required.

Although hemodialysis is not necessary in this case, it could be performed electively, given that the mean plasma half-life of ethylene glycol during fomepizole treatment is 19.7 hours. Thus, his hospital stay might be shortened. However, my practice in these cases is to forgo the risks and invasiveness of hemodialysis.

No potential conflict of interest relevant to this article was reported.

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