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Fomepizole

A New Antidote for the Treatment of Ethylene Glycol Poisoning

In this issue, Kim Bradley and Donna Lotzer present a review of fomepizole, a new medication indicated for the management of acute ethylene glycol poisoning. While it has been known for many years that this product has the ability to minimize the complications associated with ethylene glycol (and possibly methanol) ingestion, it has only recently reached the market with the support of federal grants awarded to support the development of "orphan" drug products. In 1983, the Orphan Drug Act was passed as an amendment to the Federal Food, Drug and Cosmetics Act. It provides federal funding for research and development of medications intended to diagnose or treat various rare disorders. In the act, "rare" is defined as "any disease or condition with (a) affects less than 200,000 persons in the U.S. or (b) affects more than 200,000 persons in the U.S. and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." Accidental or intentional ingestion of ethylene glycol qualifies as a rare disorder. Of the 2,192,088 human poison exposures reported to U.S. poison centers in 1997, only 4,867 involved ethylene glycol. Despite the federal subsidies for the development of fomepizole, the product has been priced by its manufacturer at nearly \$3,000 per uncomplicated course of treatment. The cost of the drug would increase dramatically if the patient required additional doses following hemodialysis.

The monograph presented here provides an illustration of a very expensive agent that may meet the Food and Drug Administration requirements for market approval (safety and efficacy), but has not borne the burden of demonstrating cost-effectiveness compared to existing therapy. Intravenous or orally administered ethanol is a well-established,

safe, efficacious and inexpensive treatment for ethylene glycol and methanol ingestion.

Fomepizole has not been well studied in adults (note the lack of clinical data presented in the monograph), has literally no data to support its use in children (of the 4,867 U.S. exposures to ethylene glycol in 1997, nearly 2,000 occurred in patients under 19 years of age), is difficult to monitor for therapeutic effectiveness, and is extremely difficult to dose, particularly in patients who require hemodialysis (the exact group of patients who might benefit the most from the product). While ethanol is associated with CNS side effects both during and after treatment, it can be monitored effectively with serum ethanol concentrations, a test routinely available in all health care facilities (and most police precincts).

The U.S. health care system has already paid enough for fomepizole through the Orphan Drug Act grants. To justify the extraordinary cost of the product, when an accepted, less expensive alternative treatment exists, fomepizole must be shown to be substantially safer or more effective than ethanol before it is adopted into routine clinical use. The recommendation of the UW Hospital and Clinics' Center for Drug Policy, and the UW Hospital Poison Control Center is that fomepizole not be added to the medication formularies of most Wisconsin health care facilities.

—Lee Vermeulen

Summary

Indications: Fomepizole (Antizol[®], Orphan Medical, Inc.) is approved by the Food and Drug Administration (FDA) as an antidote for use in actual or suspected ethylene glycol poisoning in adults. Clinical trials have not been completed for the treatment of methanol intoxication. Orphan Medical anticipates submitting a New Drug Application for this indication in 1998.¹

Monitoring Parameters: Parameters that should be monitored to evaluate the efficacy of therapy include the following: complete blood count, serum electrolytes including calcium, blood urea nitrogen, serum creatinine, glucose, urinalysis, plasma osmolality, arterial blood gases, serum pH, vital signs, plasma and urinary ethylene glycol concentrations, urine output, and electrocardiogram.^{2,3,4} In addition, the clinician should monitor for resolution of the

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patient's symptoms and for adverse effects of fomepizole. This may involve monitoring vision, neurologic status, blood pressure, heart rate, liver enzymes, and hematologic parameters such as hemoglobin, red blood cell count and white blood cell count with differential.⁵

Dose: An intravenous (IV) loading dose of 15 mg/kg is administered, followed by 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours until the blood ethylene glycol level is less than 20 mg/dl. Each dose should be diluted in at least 100 ml of normal saline or dextrose 5% solution and are administered over 30 minutes. Dosing frequency must be increased during dialysis.⁵

Pregnancy Category: C Animal reproductive studies have not been performed. Fomepizole should not be used in pregnant women unless the possible benefit outweighs the potential risks.⁵

Breast Feeding: It is not known whether fomepizole is excreted in human milk. Caution should be used when administering fomepizole to nursing mothers.⁵

Pediatrics: Efficacy and safety in pediatric patients have not been adequately studied, although clinical trials in pediatric patients are currently underway.⁵

Geriatrics: Fomepizole has not been sufficiently studied to be able to determine whether its pharmacokinetics differ in geriatric patients compared to younger patients.

Renal Impairment: When treating a renal failure patient for ethylene glycol poisoning, hemodialysis should be considered in addition to fomepizole. Because fomepizole is extensively removed by dialysis, the frequency of dosing must be increased.

Cost: The average wholesale price of fomepizole is \$1,150 for a 1.5 g vial. The average wholesale costs for a course of therapy is \$2990.

Introduction

Ethylene glycol is a colorless, odorless, sweet-tasting liquid found primarily as a component of radiator antifreeze.⁶ Ethylene glycol intoxication is relatively rare, but it can result in severe morbidity and mortality.⁷ The clinical presentation involves three stages.^{8,9} The first stage occurs 30 minutes to 12 hours post-ingestion and includes gastrointestinal complaints such as nausea and vomiting and central nervous system effects such as coma, seizures, nystagmus, and depressed reflexes. Stage two occurs 12 to 24 hours post-ingestion and presents as cardiopulmonary symptoms, including tachycardia, tachypnea, mild hypertension, congestive heart failure, and circulatory collapse. The final stage occurs 24 to 72 hours post-ingestion and is characterized by flank pain, oliguria, acute tubular necrosis, and renal failure.

Patients who have ingested a large amount of ethylene glycol commonly present with metabolic acidosis and elevated anion gap, osmolal gap, and calcium oxalate crystals in the urine.^{9,10} The metabolic acidosis and anion gap result primarily from the formation of glycolate, a metabolite of ethylene glycol. Oxalate, another metabolite of ethylene glycol, forms calcium oxalate crystals that can deposit in various tissues, resulting in renal and other tissue damage.

The standard treatment of ethylene glycol intoxication includes respiratory and circulatory support if needed, gastric decontamination, bicarbonate, thiamine, pyridoxine, hemodialysis, and ethanol.¹⁰ In severe cases, hemodialysis may be required. Ethanol blocks the metabolism of ethylene glycol by alcohol dehydrogenase. By preventing the formation of toxic metabolites via the alcohol dehydrogenase pathway, the incidence and/or severity of acidosis and tissue damage is reduced. Ethanol is administered with a goal of maintaining ethanol levels of 100 mg/dL (0.10 g/dL).²⁸ While ethanol is an effective antidote, it may enhance CNS depression, increase the risk of emesis and aspiration, and, particularly in children, increase the risk of apnea and hypoglycemia. Fomepizole is an alternative to ethanol because it blocks the metabolism of ethylene glycol by alcohol dehydrogenase without the toxic effects. Either ethanol or fomepizole therapy is indicated in patients with a documented serum ethylene glycol level greater than or equal to 20 mg/dL or in patients suspected of ingesting toxic amounts of ethylene glycol. For ethylene glycol levels of 50 mg/dL or greater hemodialysis is recommended as an adjunctive therapy.²⁸ Hemodialysis may also be recommended in patients with ethylene glycol levels less than 50 mg/dL if the patient presents with oliguria, anuria, azotemia, uncompensated or severe metabolic acidosis, or gross hematuria in the presence of urinary calcium oxalate crystals.

Pharmacology/Pharmacokinetics

Fomepizole has been demonstrated to be a potent competitive inhibitor of alcohol dehydrogenase in both human and animal studies.⁵ Alcohol dehydrogenase is the enzyme that catalyzes the initial step in the major pathway responsible for the metabolism of ethylene glycol to glycolate and other toxic metabolites.^{5,11} It is important to note, however, that blockade of alcohol dehydrogenase may result in the accumulation of toxic metabolites produced via alternate, uninhibited enzyme pathways. As a result, hemodialysis or other therapies may be needed in addition to fomepizole in cases of severe ethylene glycol intoxication.¹¹

Absorption

Fomepizole is available only as a formulation for IV administration. Studies in healthy male volunteers reported

that oral doses of fomepizole (7 to 50 mg/kg) were rapidly absorbed.^{4,12} After a single oral dose of 10 to 100 mg/kg, peak plasma concentrations were achieved within 0.5 to 2 hours.¹² The time to peak plasma concentrations is similar for both oral and IV administration. In a crossover study in healthy male subjects, plasma levels of fomepizole after IV and oral dosing were nearly identical from 15 minutes until 25 hours after dosing.¹³

Distribution

Fomepizole distributes rapidly in total body water. The volume of distribution of fomepizole varies from 0.6 L/kg to 1.02 L/kg.^{5,14,15} No human studies have examined the extent of plasma protein binding of fomepizole. One study conducted in dogs did report a low degree of plasma protein binding.^{12,14}

Metabolism and excretion

Fomepizole is metabolized in the liver to multiple inactive or weakly active metabolites, including 4-carboxypyrazole, 4-hydroxymethylpyrazole, and the N-glucuronide conjugates of these metabolites.^{11,12} Multiple enzyme systems, including cytochrome P450 2E1, are thought to be responsible for the metabolism of fomepizole.^{14,16}

Only 1.4 to 3.5% of a single dose of fomepizole is renally excreted unchanged in the urine.^{5,12} Significantly more of the primary metabolite 4-carboxypyrazole is excreted in the urine. In a study conducted by Jacobsen and colleagues, 4-carboxypyrazole excretion in the urine accounted for greater than 50% of the fomepizole dose.¹⁴

After the rapid distribution phase, fomepizole is eliminated from the body by zero order processes, even at IV doses as low as 5 mg/kg and oral doses of 10 mg/kg.^{12,14,17} This suggests saturation of the major elimination pathway even at low doses. A dose-ranging study conducted by Jacobsen and colleagues demonstrated that higher doses of fomepizole are associated with more rapid elimination of fomepizole.¹² This increase in elimination rate with dose is not predicted by Michaelis-Menten kinetics. One explanation is that at higher doses, an alternate low-affinity, high-capacity system more significantly contributes to the elimination of fomepizole.¹²

In a multiple dose study conducted by Jacobsen and colleagues, the rate of elimination of fomepizole was increased after several doses.¹⁸ This indicates that fomepizole probably autoinduces its own metabolism, and a larger dose may be necessary to maintain therapeutic plasma levels with multiple doses.

Concomitant administration of ethanol and fomepizole reduces the elimination of both drugs. A study in healthy human volunteers found that fomepizole in doses of 10 to 20 mg/kg, which corresponded to plasma concentrations of 120

to 260 micromole/L, was found to decrease the rate of decline of ethanol concentration by 40%.¹⁴ Ethanol, in turn, was found to reduce the rate of decline of fomepizole concentration by 50%, an effect not apparent until 8 hours after dosing.

Blood level measurement

The manufacturer specifically states that it is unnecessary to measure fomepizole levels during therapy. Based on limited kinetic data, fomepizole blood levels greater than 10 micromole/L have been shown to provide inhibition of alcohol dehydrogenase. Burns showed in a patient poisoned with methanol and treated with fomepizole that blood levels fluctuated greatly with the approved dosing regimen, with a range of from 150 - 450 micromoles/L.¹⁷

Clinical Trials

There are no published prospective, randomized clinical trials either using fomepizole alone or comparing the use of fomepizole to ethanol for the treatment of ethylene glycol intoxication.

Unpublished prospective clinical study

An open-label, uncontrolled, multicenter, prospective study was conducted in 16 patients with suspected or confirmed ethylene glycol poisoning. The majority of patients (10 of 16) presented in the late stages of the clinical course.⁵ The median baseline blood ethylene glycol concentration was 119.5 mg/dl. Patients received an IV loading dose of fomepizole of 15 mg/kg, followed by 10 mg/kg IV every 12 hours for four doses, followed by 15 mg/kg IV every 12 hours until the serum ethylene glycol concentration was less than 20 mg/dl. For the 14 patients that required dialysis, fomepizole was given every 4 hours during dialysis. Urinary oxalate levels, the clinical condition of the patient, and plasma ethylene glycol, glycolate, and fomepizole levels were monitored. All patients presenting with elevated glycolate levels had a rapid reduction in these levels with the initiation of fomepizole therapy, and all patients had non-detectable levels at the time of discharge. In patients who initially presented with non-detectable levels of plasma glycolate, the levels remained non-detectable throughout therapy. Similar findings were achieved with urinary oxalate levels. Initially, fomepizole's effect on glycolate and oxalate levels was confounded by hemodialysis and high ethanol levels in the majority of patients. However, after hemodialysis and when serum ethanol had declined to insignificant levels, fomepizole alone appeared to be effective at blocking any increase in oxalate and glycolate levels. Five of 12 patients with low baseline serum bicarbonate continued to have low bicarbonate at endpoint, but most had clinical improvement. Nine of 11 patients with low baseline

blood pH had a normal pH at endpoint. Among the 16 enrolled patients, two died. One patient died of a myocardial infarction and the second died of cerebral herniation and edema. Both deaths were considered a consequence of the ethylene glycol toxicity. Of the 14 patients who survived, eight were alive without sequelae at the end of the trial and six were alive with sequelae. Sequelae included reversible acute renal failure or renal insufficiency, pleural effusion, anemia, and/or psychiatric abnormalities.

Unpublished retrospective clinical study

An open-label, uncontrolled, retrospective study was conducted in 26 patients with suspected ethylene glycol poisoning.⁵ The median baseline blood ethylene glycol concentration was 10.4 mg/dL (range 1 to 831 mg/dL). Fomepizole was administered orally in eight patients, intravenously in 17 patients, and both orally and intravenously in one patient. Fomepizole loading doses ranged from 0.2 to 19.5 mg/kg, and five of 26 patients underwent hemodialysis. There were five patients who presented with normal renal function and insignificant blood ethanol levels. These patients maintained normal renal function throughout therapy with fomepizole treatment alone. One of the 26 patients died as a result of complications of metabolic acidosis, and 19 of 26 patients were alive without sequelae at discharge. Sequelae, including renal insufficiency, hepatitis, and/or amnesic aphasia and dysphasia, were present in only four patients at discharge. Of the 12 patients with abnormal bicarbonate levels at baseline, two patients still had a bicarbonate deficit after treatment. Eight patients actually experienced an overcorrection of their bicarbonate levels. Of the eight patients who had an acidic blood pH at baseline, one had acidemia at endpoint, and four patients were over corrected to an alkalotic blood pH.

Trial available in abstract form only

Brent and colleagues conducted a trial in which 15 patients, ranging in age from 19 to 73, with a mean baseline ethylene glycol level of 161 mg/dL (range 5 to 400 mg/dL) were treated with both fomepizole and hemodialysis.¹⁹ The results reported were as follows: serum glycolate levels fell in all patients with treatment, 11 patients fully recovered, two patients had resolving acute renal failure when they were lost to follow-up, and two patients died (one of cerebral edema and herniation and one of cardiogenic shock following a myocardial infarction). No patient with a normal serum creatinine at presentation developed renal injury. From the information presented in the abstract, it is difficult to determine whether the benefit to the patient was because of fomepizole or hemodialysis.

Case studies

Baud and colleagues reported the clinical course of three

patients treated with fomepizole for ethylene glycol ingestion.²⁰ Two of the patients received fomepizole only, no dialysis nor ethanol was administered. The other patient did not receive dialysis, but did receive a 5.4 g dose of ethanol which had been eliminated from the bloodstream by the time fomepizole therapy was initiated. The blood ethylene glycol concentrations at presentation were 60 mg/dL (15 hours after ingestion), 81 mg/dL (4 hours after ingestion), and 150 mg/dL (3 hours after ingestion). The fomepizole dosing regimen employed was an initial dose of 15 to 20 mg/kg orally or by nasogastric tube, followed by 5 to 10 mg/kg every 12 hours until it was deemed no longer necessary. In 2 patients, treatment with fomepizole plus bicarbonate resulted in normalization of the anion gap and resolution of acidosis. These patients had a normal serum creatinine at presentation, which was maintained throughout treatment. One patient had numerous urinary oxalate crystals at the start of therapy, but they disappeared within 53 hours after the initiation of therapy. In the one patient presenting with normal bicarbonate, anion gap, and serum creatinine levels the serum creatinine remained within normal limits and metabolic acidosis never developed during therapy. The plasma half-life of ethylene glycol was elevated in these patients from a normal half-life of 3 hours to about 17 hours. This indicates inhibition of ethylene glycol metabolism by fomepizole. The only side effect observed was a skin rash in one patient and a possible eosinophilia in the other two patients.

A case report of a 42 year old man who presented to the hospital 4.5 hours after ingestion of antifreeze was described by Galliot and colleagues.²¹ Fomepizole was administered as an IV infusion and the dosing schedule was as follows (all times indicated as hours after ingestion of ethylene glycol): 9.5 mg/kg at 9 hours, 7.0 mg/kg at 21 hours, 3.6 mg/kg at 33 hours, 1.2 mg/kg at 45 hours, and 0.6 mg/kg at 57 hours. The patient received a single 45 g intravenous dose of ethanol prior to fomepizole therapy, and the blood ethanol level was 0.12 g/L upon initiation of fomepizole. No hemodialysis was performed. The anion gap returned to normal within 4 hours of initiation of fomepizole and the rate of excretion of oxalate normalized on the second day of therapy. The patient's metabolic acidosis resolved and did not recur, and the serum creatinine remained normal throughout therapy. The plasma half-life of ethylene glycol was elevated to 12 hours, indicating inhibition of its metabolism. No side effects of therapy were noted in this patient.

A 30 year old, 74 kg man who ingested 100 g of ethylene glycol was described by Harry and colleagues.²² Fomepizole therapy was initiated with an IV loading dose of 16.2 mg/kg administered over 30 minutes. Subsequent doses adminis-

tered every 12 hours were 8.1 mg/kg, 5.4 mg/kg, 2.7 mg/kg, and 1.4 mg/kg. This patient received no dialysis nor ethanol therapy, and had no detectable blood ethanol at presentation. The patient's elevated anion gap and metabolic acidosis disappeared within 4 hours. Urinary oxalate excretion remained normal during the first 20 hours of therapy, and serum calcium levels also remained in the normal range. The half-life of ethylene glycol was prolonged to 16 hours during fomepizole therapy, suggesting reduced hepatic metabolism of ethylene glycol. The only side effect observed was a slight increase in serum transaminase activity.

Faessel and colleagues described two patients with ethylene glycol intoxication who were treated with fomepizole, ethanol, and hemodialysis.²³ The first patient, a 95 kg man, received a 64 g dose of ethanol via nasogastric tube upon presentation 36 hours after ethylene glycol ingestion. He then received a 16 mg/kg IV dose of fomepizole over 4.25 hours, followed immediately by a second 16 mg/kg dose administered over 45 minutes. Two hours after a 4-hour dialysis session, this patient received a final 8.4 mg/kg dose of fomepizole. This patient's clinical course was uneventful after initiation of treatment, although he required eight hemodialysis sessions because of anuric renal failure. The second patient, a 58 kg man, received a total of 51.2 g of ethanol via nasogastric tube upon presentation to the hospital 6 hours after ingestion of ethylene glycol. Patient 2 received an 11.2 mg/kg IV dose of fomepizole administered over 45 minutes, followed by an 11.2 mg/kg dose every 12 hours until a total dose of 2.05 g had been given. This patient required three hemodialysis sessions during fomepizole therapy before his renal function returned to normal. These two cases demonstrated that fomepizole is dialyzable and dosage adjustments are necessary during dialysis to maintain therapeutic blood levels.

Two patients who were found in a comatose state after ingestion of ethylene glycol were described by Jobard and colleagues.¹⁵ The patients' plasma ethylene glycol levels at presentation were 51 mg/dL and 350 mg/dL, respectively. Neither patient received ethanol treatment nor had detectable ethanol levels at presentation, but both patients did receive hemodialysis. About 17 hours after ingestion of ethylene glycol, an IV loading dose of 10 mg/kg of fomepizole was infused over 30 minutes to patient 1. A second infusion of 2.5 mg/kg/hr was administered during dialysis. The patient required daily hemodialysis sessions for 8 days because of persistent anuria, but complete recovery was observed at discharge after a 14 day hospital stay. No adverse effects of fomepizole therapy were noted in this patient. Patient 2 received a fomepizole loading dose of 20 mg/kg infused over 30 minutes, followed by a maintenance

dose of 1.5 mg/kg/hr during an 8 hour hemodialysis session. Despite two hemodialysis sessions and symptomatic treatment, patient 2 died 48 hours after admission because of multiorgan failure and disseminated intravascular coagulation. During dialysis, the plasma fomepizole concentration in patient 1 fell rapidly despite an additional dose of fomepizole. In contrast, the continuous fomepizole infusion that patient 2 received during dialysis was able to successfully maintain a therapeutic fomepizole level.

Adverse Effects

Fomepizole has been found to have less toxicity than the parent compound, pyrazole. The following side effects are those that have been reported in patients treated with fomepizole. The most common adverse effects are headache (12%), nausea (11%), and dizziness (7%).⁵ Other adverse reactions that were reported to occur in 6% or fewer patients include the following:^{4,5,13,16,18,20}

Nervous: dizziness, lightheadedness, vertigo, feeling of motion sickness, drunken feeling, headache, mild speech and visual disturbances, loss of appetite, nystagmus, decreased environmental awareness

Digestive: diarrhea, nausea, anorexia, heartburn, abdominal pain

Cardiovascular: bradycardia, tachycardia, hypotension

Hemic/Lymphatic: eosinophilia, lymphangitis, anemia

Skin: phlebosclerosis with intravenous dosing, rash with pruritus

Respiratory: hiccups, pharyngitis

Sensory: bad/metallic taste, blurred vision, abnormal smell

Body as a whole: fever, somnolence, hangover, lumbalgia

In addition, some laboratory value alterations have been reported with fomepizole therapy. These include mild, transient elevations in liver enzymes, serum triglycerides and/or cholesterol, serum bilirubin, serum uric acid, and eosinophils.^{4,5,16,18,20} As with the adverse effects listed, it is not known whether these laboratory alterations are definitely associated with fomepizole use. Several laboratory abnormalities, such as those associated with anemia or azotemia, may be caused by the toxins ingested rather than by the treatment with fomepizole.⁵

Currently, ethanol is the preferred (although never formally FDA-approved) drug therapy for the treatment of ethylene glycol intoxication. Potential problems with ethanol therapy include hypoglycemia, intoxication, central nervous system depression, hepatotoxicity, dehydration, and fluctuating serum levels.^{24,25} The potential adverse effects of ethanol and fomepizole cannot be compared directly because many of the side effects with fomepizole were reported in healthy individuals, while the side effects of

ethanol were those experienced in patients who had ingested ethylene glycol. Patients who receive fomepizole therapy to treat ethylene glycol intoxication may report a different severity, frequency, or type of side effect than those reported in healthy individuals.

Overdose

In a study conducted by Jacobsen and colleagues, six of seven healthy volunteers who received 50 or 100 mg/kg of fomepizole reported side effects of therapy.⁴ These doses are three to six times the usual doses used to treat ethylene glycol poisoning. Although dizziness and nausea were most frequently reported, mild speech and visual disturbances, a "feeling of drunkenness," loss of appetite, vertigo, headache, and nystagmus were also reported. The central nervous system effects were of brief duration in most patients, but symptoms did last 30 hours in one patient.

Drug interactions

As previously mentioned, therapeutic doses of fomepizole (10-20 mg/kg) in healthy subjects resulted in a reduced elimination rate of ethanol.¹⁴ Mutual inhibition of fomepizole elimination by ethanol occurred in these same patients.

Because fomepizole is metabolized by cytochrome P450, it may interact with drugs that induce or inhibit the cytochrome P450 enzyme system.⁵ While there are no known interactions of this type, patients should be monitored for alterations in side effects and efficacy when administered with drugs metabolized by this route.

Cost, Dose, and How Supplied

The recommended dosing schedule was chosen on the basis of a single unpublished, open-label study in patients with ethylene glycol poisoning.⁵ In that study, fomepizole was dosed to maintain therapeutic blood levels of 100 to 300 micromoles/L, however routine serum fomepizole concentrations are not routinely measured in most institutions, and serum concentration is not a practical therapeutic tool for dose adjustment. The usual dosing schedule is a loading dose of 15 mg/kg IV, followed by doses of 10 mg/kg every 12 hours for four doses, then 15 mg/kg every 12 hours until the ethylene glycol level is less than 20 mg/dL.⁵ The doses should be based on actual body weight, rather than ideal weight.²⁷ The dose should be injected into at least 100 ml of normal saline or dextrose 5% solution, and the resultant mixture infused over 30 minutes.⁵ Fomepizole should never be given undiluted or by bolus injection because of the risk of venous irritation and phlebosclerosis.

Because fomepizole is extensively removed by dialysis, the frequency of dosing must be increased in patients receiving hemodialysis.^{5,15} Based on two case reports, Jobard and colleagues recommended a fomepizole loading dose of

10 to 20 mg/kg, followed by continuous infusion of 1 to 1.5 mg/kg/hr throughout the duration of hemodialysis in patients receiving concurrent fomepizole therapy.¹⁵ Again, it must be emphasized that it is not practical to obtain serum fomepizole concentrations for use in adjusting the therapeutic dose in patients being treated. The manufacturer does recommend the following dosing schedule for patients receiving hemodialysis:⁵

Dose at the beginning of hemodialysis

If <6 hours since last fomepizole dose—do not administer dose

If ≥6 hours since last fomepizole dose—administer next scheduled dose

Dosing during hemodialysis

Dose every 4 hours

Dosing at the time hemodialysis is completed

Time between last dose and the end of hemodialysis

<1 hour do not administer dose at the end of hemodialysis

1 to 3 hours administer one-half of next scheduled dose

>3 hours administer next scheduled dose

Maintenance dosing off hemodialysis

Give next scheduled dose 12 hours from last dose administered

Fomepizole is available in 1.5 mL vials containing 1 g/mL. The average wholesale price for fomepizole for 1.5 g vial is \$1150. The average wholesale cost for a course of therapy is \$2,990. The cost of a comparable dose of ethanol for intravenous administration is \$10.56.

Recommendation

Fomepizole is an enormously expensive drug, currently approved for use only in a limited segment of the population: adults who are experiencing ethylene glycol intoxication. Fomepizole is not approved for use in pediatric patients, and no published reports have addressed pediatric dosing thus far. The amount of published literature regarding fomepizole is extremely limited. Currently, published reports of fomepizole for ethylene glycol poisoning consist only of case reports. Two unpublished studies have demonstrated that patients treated with fomepizole improve clinically with minimal side effects of treatment. However, both studies were confounded by either hemodialysis or by high ethanol blood levels at presentation. There is no evidence to

date that supports a greater efficacy or less toxicity for fomepizole compared to ethanol because no comparative studies have been conducted.

In order to effectively manage patients with an ethylene glycol overdose, hospitals must be able to monitor ethylene glycol levels, anion gap, plasma osmolality, arterial blood gases and serum pH. If a hospital is unable to perform these laboratory tests, they should immediately refer suspected ethylene glycol overdoses to institutions able to provide the appropriate monitoring. Additionally, a treating hospital should be able to provide hemodialysis if needed. Because of its high cost and the need for specialized laboratory monitoring, fomepizole should only be stocked by hospitals capable of performing the required laboratory tests. This means that for many smaller hospitals, there is no need to add fomepizole to the formulary, as they may not have available the technology necessary to appropriately monitor patients exposed to ethylene glycol. It is recommended that fomepizole be added to the medication formulary only at larger, referral hospitals. Smaller institutions who feel it necessary to have alcohol dehydrogenase inhibition therapy available for patients who present to their facilities prior to transport to referral centers should consider maintaining ethanol (either in intravenous or oral formulation) for use prior to transport.

In all cases, clinicians should consult a poison center prior to the initiation of fomepizole therapy. Clinicians are encouraged to contact the Wisconsin Poison System which operates through the poison control centers at Children's Hospital of Wisconsin in Milwaukee, and the University of Wisconsin Hospital and Clinics in Madison. Medical toxicologists provide 24 hour a day physician back-up for the staff of the two centers. The toll-free phone number for either center in Wisconsin is 1-800-815-8855. ■

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