FOMEPIZOLE FOR THE TREATMENT OF ETHYLENE GLYCOL POISONING

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ABSTRACT

Background Ethylene glycol poisoning causes metabolic acidosis and renal failure and may cause death. The standard treatment is inhibition of alcohol dehydrogenase with ethanol, given in intoxicating doses, and adjunctive hemodialysis. We studied the efficacy of fomepizole, a new inhibitor of alcohol dehydrogenase, in the treatment of ethylene glycol poisoning.

Methods We administered intravenous fomepizole to 19 patients with ethylene glycol poisoning (plasma ethylene glycol concentration, ≥20 mg per deciliter [3.2 mmol per liter]). Patients who met specific criteria also underwent hemodialysis. Treatment was continued until plasma ethylene glycol concentrations were less than 20 mg per deciliter. Acid–base status, renal function, the kinetics of fomepizole, and ethylene glycol metabolism were assessed at predetermined intervals.

Results Fifteen of the patients initially had acidosis (mean serum bicarbonate concentration, 12.9 mmol per liter). Acid–base status tended to normalize within hours after the initiation of treatment with fomepizole. One patient with extreme acidosis died. In nine patients, renal function decreased during therapy; at enrollment, all nine had high serum creatinine concentrations and markedly elevated plasma glycolate concentrations (≥97.7 mg per deciliter [12.9 mmol per liter]). None of the 10 patients with normal serum creatinine concentrations at enrollment had renal injury during treatment; all 10 had plasma glycolate concentrations at or below 76.8 mg per deciliter (10.1 mmol per liter). Renal injury was independent of the initial plasma ethylene glycol concentration. The plasma concentration of glycolate and the urinary excretion of oxalate, the major metabolites of ethylene glycol, uniformly fell after the initiation of fomepizole therapy. Few adverse effects were attributable to fomepizole.

Conclusions In patients with ethylene glycol poisoning, fomepizole administered early in the course of intoxication prevents renal injury by inhibiting the formation of toxic metabolites. (N Engl J Med 1999; 340:832-8.)

ETHYLENE glycol poisoning may cause severe morbidity and death.[1] Though not toxic itself, ethylene glycol is converted by alcohol dehydrogenase to active metabolites[1,2] (Fig. 1) that cause metabolic acidosis, renal failure, hypocalcemia, oxaluria, damage to the central nervous system and cranial nerves, and cardiovascular instability.[3]

Standard treatments for ethylene glycol poisoning are hemodialysis and inhibition of alcohol dehydrogenase,[1,4] the latter by the intravenous or oral administration of high (intoxicating) doses of ethanol. The accepted target plasma ethanol concentration is 100 to 125 mg per deciliter (21.7 to 27.1 mmol per liter).[1] Since patients are treated with large doses of ethanol and become intoxicated, they must be closely monitored. If ethanol therapy is prolonged, patients are also at risk for hepatotoxicity and hypoglycemia. In addition, the kinetics of ethanol metabolism are unpredictable, so blood ethanol concentrations must be measured frequently, and the dose of ethanol adjusted accordingly.[5,6]

Fomepizole (4-methylpyrazole) is an inhibitor of alcohol dehydrogenase that appears to have none of the adverse effects of ethanol on administration.[1,2,7-11] In animals, fomepizole inhibits alcohol dehydrogenase[1,8] and is an effective treatment for ethylene glycol poisoning.[1,3] It has also proved effective, in nine cases, for the treatment of ethylene glycol poisoning in humans.[12-16] We report the results of a prospective study of fomepizole in the treatment of 19 patients with ethylene glycol poisoning.

METHODS

Between November 1995 and August 1997, we studied 23 consecutive patients with confirmed or possible ethylene glycol poisoning. Three other patients were not enrolled because we were unable to obtain consent from one and were not alerted to the cases of two other patients.

The criteria for enrollment were an age of at least 12 years and one of the following three sets of characteristics: a plasma ethylene glycol concentration of at least 20 mg per deciliter (3.2 mmol

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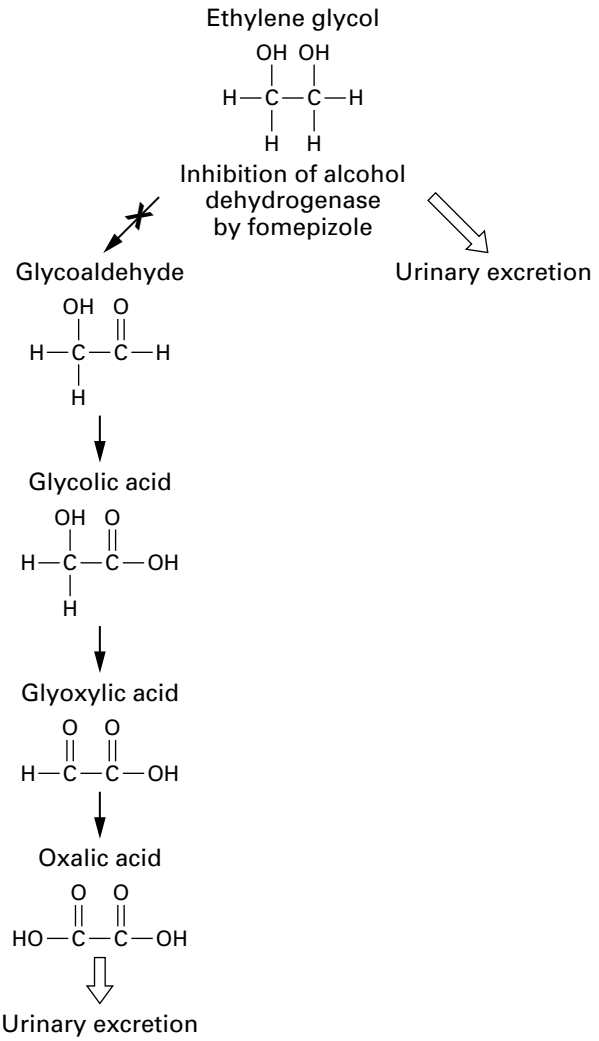


Figure 1. Metabolism of Ethylene Glycol and Inhibition of Alcohol Dehydrogenase by Fomepizole.

per liter); suspected ingestion of ethylene glycol and three of four specific laboratory findings (an arterial pH below 7.3, a serum bicarbonate concentration less than 20 mmol per liter, a serum osmolar gap greater than 10 mOsm per liter, and oxaluria); or suspected ingestion of ethylene glycol within the preceding hour and a serum osmolar gap greater than 10 mOsm per liter. The exclusion criteria were the administration of ethanol at the participating hospital, known reactions to pyrazoles, and pregnancy; no patients were excluded on the basis of these criteria.

The study was approved by the appropriate institutional review boards at all the participating centers. Written informed consent was obtained from the patient if he or she was lucid; otherwise, consent was obtained from the closest available relative or legal guardian, or if neither was available, from two physicians uninvolved with the trial.

Treatment Protocol

Fomepizole (Antizol, provided by Orphan Medical, Minnetonka, Minn.) was administered intravenously in a loading dose of 15 mg per kilogram of body weight, followed by 10 mg per kilogram every 12 hours for 48 hours, after which the dose was increased to 15 mg per kilogram every 12 hours to compensate for increased fomepizole metabolism.[17] These doses were based on preclinical studies.[11,17] The patients were treated with fomepizole until the plasma ethylene glycol concentration was less than 20 mg per deciliter.

After the loading dose of fomepizole had been administered, hemodialysis was begun for any of the following reasons: an arterial pH below 7.1, a decrease of more than 0.05 in the arterial pH despite the intravenous administration of sodium bicarbonate, an arterial pH below 7.3 despite the intravenous administration of sodium bicarbonate, a decrease in the serum bicarbonate concentration of more than 5 mmol per liter despite bicarbonate therapy, a serum creatinine concentration greater than 3 mg per deciliter (265 μmol per liter), an increase in the serum creatinine concentration of 1 mg per deciliter (88 μmol per liter) or more, or an initial plasma ethylene glycol concentration of 50 mg per deciliter (8.1 mmol per liter) or greater.

Monitoring of Patients

The patients received continuous cardiac monitoring during the trial. Investigators examined all the patients daily. Complete blood counts and measurements of serum electrolytes, urea nitrogen, creatinine, calcium, liver-function values, plasma ethylene glycol, and arterial-blood gases were performed at the participating centers at enrollment and at predetermined intervals ranging from 2 to 24 hours during the trial. Electrocardiography and urinalysis were performed every 24 hours. Urinary volume was measured every 12 hours, and aliquots of each sample were assayed for oxalate at the reference laboratory.[18] If there was a delay between the initial presentation at the hospital and enrollment in the trial, the measurements of serum electrolytes, urea nitrogen, arterial pH, and plasma glycolate and ethylene glycol were repeated one hour or less before treatment with fomepizole was begun. All the patients also underwent comprehensive toxicology screening at the time of enrollment.

Plasma concentrations of ethylene glycol, glycolate (the predominant circulating metabolite of ethylene glycol), ethanol, and fomepizole were measured at the reference laboratory at Louisiana State University Medical Center, as previously described.[19-21] The values of plasma ethylene glycol determined locally were used to guide the administration of fomepizole. The values presented in this report were determined at the reference laboratory.

The investigators at the participating centers documented any adverse effects, including the date of onset, intensity, relation to fomepizole, and outcome.

End Points

The end points of the study were the development of renal injury (high serum creatinine concentrations), additional production of ethylene glycol metabolites (an increase in either the plasma glycolate concentration or the urinary excretion of oxalate after the administration of fomepizole), and the development of cranial neuropathies. Patients with high serum creatinine concentrations were followed as outpatients until the values had returned to normal.

Statistical Analysis

Data entered on case-report forms by investigators at the participating centers were verified by a study nurse who visited each site and reviewed medical records. Mean values were compared with the use of Student's unpaired t-tests. The correlation between arterial pH values and plasma glycolate concentrations was determined by calculating Pearson's correlation coefficient.

RESULTS

Among the 23 patients initially enrolled in the study, 4 who met the criteria for enrollment were subsequently found not to have plasma ethylene gly-

TABLE 1. BASE-LINE CHARACTERISTICS OF 19 PATIENTS WITH ETHYLENE GLYCOL POISONING.*

CHARACTERISTIC	ALL PATIENTS (N=19)	PATIENTS WITH RENAL INJURY (N=9)	PATIENTS WITHOUT RENAL INJURY (N=10)	P VALUE†
Sex (F/M)	2/17	1/8	1/9	
Age (yr)				0.55
Mean	41	43	40	
Range	19–73	28–60	19–73	
Time from ingestion of ethylene glycol to treatment with fomepizole (hr)‡				0.004
Mean	11.4	15.1	9.6	
Range	6.6–20.8	9.0–20.8	6.6–13.9	
Plasma ethylene glycol (mg/dl)				0.34
Mean	123	99	144	
Range	24–446	24–213	26–446	
Plasma glycolate (mg/dl)				<0.001
Mean	89.7	159	28.1	
Range	0–264.4	97.7–264.4	0–76.8	
Serum creatinine (mg/dl)				<0.001
Mean	1.5	2.2	0.9	
Range	0.6–3.3	1.5–3.3	0.6–1.2	
Arterial pH§				0.003
Mean	7.24	7.14	7.34	
Range	6.93–7.47	6.93–7.35	7.16–7.47	
Serum bicarbonate (mmol/liter)				<0.001
Mean	12.9	6.8	17.8	
Range	4.0–28.0	4.0–9.8	5.0–28.0	
Plasma ethanol (mg/dl)				0.87
Mean	60	63	58	
Range	0–181	0–181	0–172	

*To convert the values for plasma ethylene glycol to millimoles per liter, multiply by 0.161. To convert the values for plasma glycolate to millimoles per liter, multiply by 0.132. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for plasma ethanol to millimoles per liter, multiply by 0.217.

†The P value is for the comparison between patients with renal injury and those without renal injury.

‡Time to treatment was unknown for four patients with renal injury.

§Arterial pH was not determined in one patient who did not have renal injury.

col concentrations greater than 20 mg per deciliter or not to meet other criteria for entry. Three of them did not have ethylene glycol poisoning; one had alcoholic ketoacidosis, one had acetaminophen poisoning, and one had a misdiagnosis of ethylene glycol poisoning (laboratory error). The fourth patient was excluded because her initial plasma ethylene glycol concentration was 9.7 mg per deciliter (1.6 mmol per liter). These four patients were given fomepizole and were included only in the analyses of adverse events and pharmacokinetics. The mean (±SD) age of the 23 patients was 42±12 years and that of the 19 patients in the analysis of efficacy was 41±13 years (Table 1).

Fourteen of the 19 patients had consumed radiator antifreeze. The source of ethylene glycol in the other patients could not be determined. One patient had also ingested 150 mg of doxepin, one had ingested 300 mg of cyclobenzaprine, one had taken cocaine, and one had drunk gasoline. In 12 patients plasma ethanol was detectable, in 4 of them at concentrations greater than 100 mg per deciliter (21.7 mmol per liter). Twelve patients had oxalate crystaluria and eight had microscopical hematuria.

Characteristics at Presentation

At presentation, 7 of the 19 patients were awake, 7 were comatose, 3 were inebriated, and 2 were lethargic. Nine patients had high serum creatinine concentrations, and 15 had metabolic acidosis and low serum bicarbonate concentrations (Table 1). The initial arterial pH value was inversely correlated with the plasma glycolate concentration ($r=-0.84$, $P<0.001$) (Fig. 2).

Clinical Course

Seventeen patients underwent hemodialysis. The 19 patients were given an average of 3.5 doses of fomepizole (range, 1 to 7) over an average of 17.8 hours (range, 5 to 58). Plasma glycolate concentrations decreased progressively in all the patients (Fig. 3A). Concomitantly, arterial pH values and serum bicarbonate concentrations increased progressively (Fig. 3B and 3C, respectively). Clinical improvement was correlated with the normalization of acid–base status. None of the patients had a spontaneous deterioration in mental status or hypoglycemia after the initiation of therapy. The plasma fomepizole concentration during therapy usually ranged from

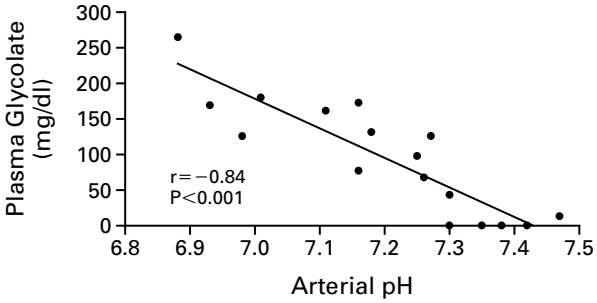


Figure 2. Plasma Glycolate Concentrations in Relation to Arterial pH at the Time of Enrollment in 18 Patients with Ethylene Glycol Poisoning.

Plasma glycolate and pH were measured within one hour of each other. The line was determined by least-squares regression analysis. To convert the values for plasma glycolate to millimoles per liter, multiply by 0.132. Seventeen data points are shown because 2 of these 18 patients had overlapping values.

15 to 30 μg per milliliter (183 to 366 μmol per liter), but occasionally, the values were lower. The mean half-time of elimination of ethylene glycol from plasma was 19.7±1.3 hours. None of the patients in whom plasma glycolate concentrations were undetectable at enrollment had measurable concentrations during therapy. Urinary oxalate excretion decreased in all the patients during treatment with fomepizole. Data from two representative patients are shown in Figure 4.

Outcome

Eighteen of the 19 patients survived their acute illness. The patient who died had an arterial pH of 7.05 and an acute myocardial infarction before enrollment. He died from cardiogenic shock 22 hours later. None of the patients had cranial neuropathy.

All nine patients with high serum creatinine concentrations at enrollment had a further increase (peak value, 2.4 to 14.7 mg per deciliter [212 to 1299 μmol per liter]) during treatment. These nine patients presented later and had more severe acidosis at the time of presentation than those who had normal serum creatinine concentrations. The serum creatinine concentration became normal in six of the nine patients, and ranged from 1.5 to 3.8 mg per deciliter (133 to 336 μmol per liter) in the other three patients at the time of the last measurement. All the patients in whom renal injury developed had plasma glycolate concentrations of at least 98 mg per deciliter (12.9 mmol per liter) at enrollment. No signs of renal injury developed in any patient whose initial plasma glycolate concentration did not exceed 76.8 mg per deciliter (10.1 mmol per liter) or whose initial serum creatinine concentration was normal.

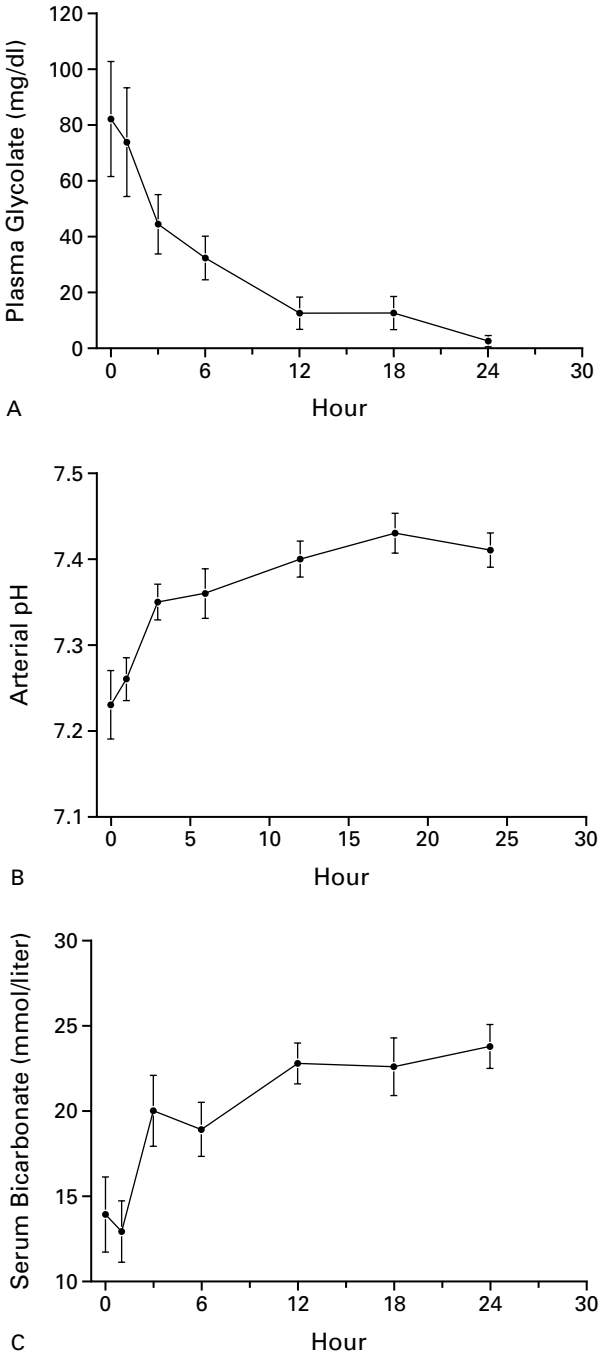
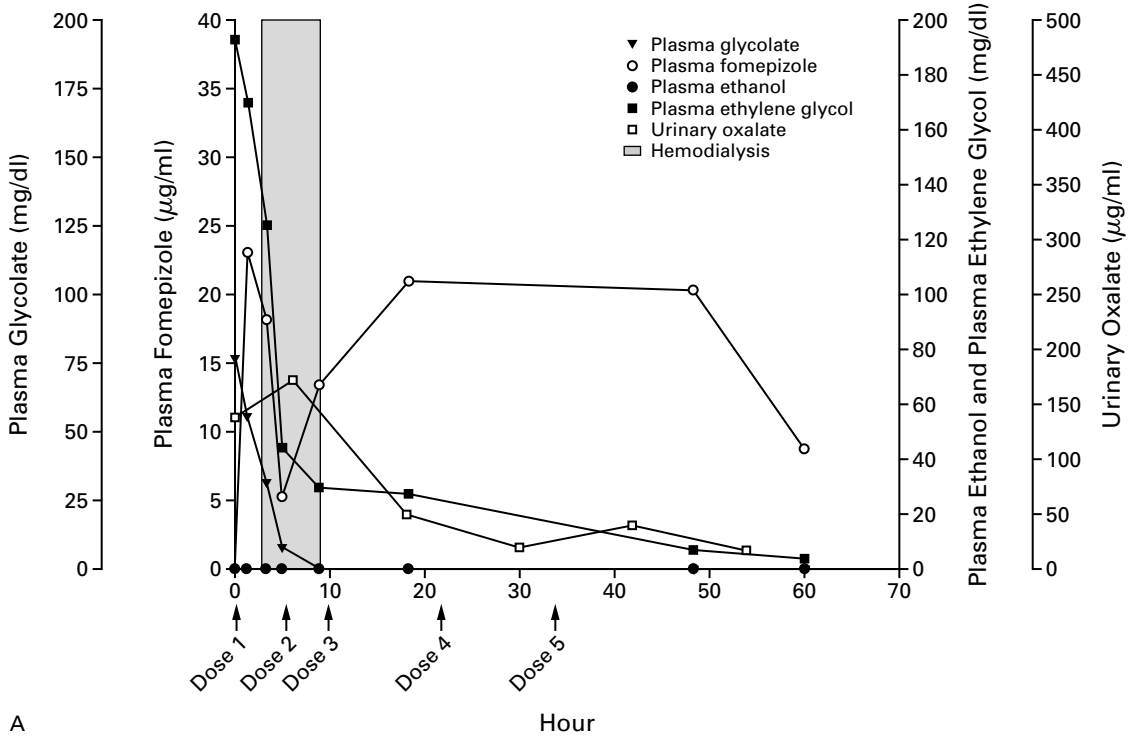


Figure 3. Mean (±SE) Plasma Glycolate Concentrations (Panel A), Arterial pH (Panel B), and Serum Bicarbonate Concentrations (Panel C) over Time during the First Day of Fomepizole Therapy in 19 Patients with Ethylene Glycol Poisoning.

The value at time zero was obtained within an hour before the initiation of fomepizole therapy. The plasma glycolate values are for the 14 patients in whom plasma glycolate was detected at enrollment. To convert plasma glycolate values to millimoles per liter, multiply by 0.132.



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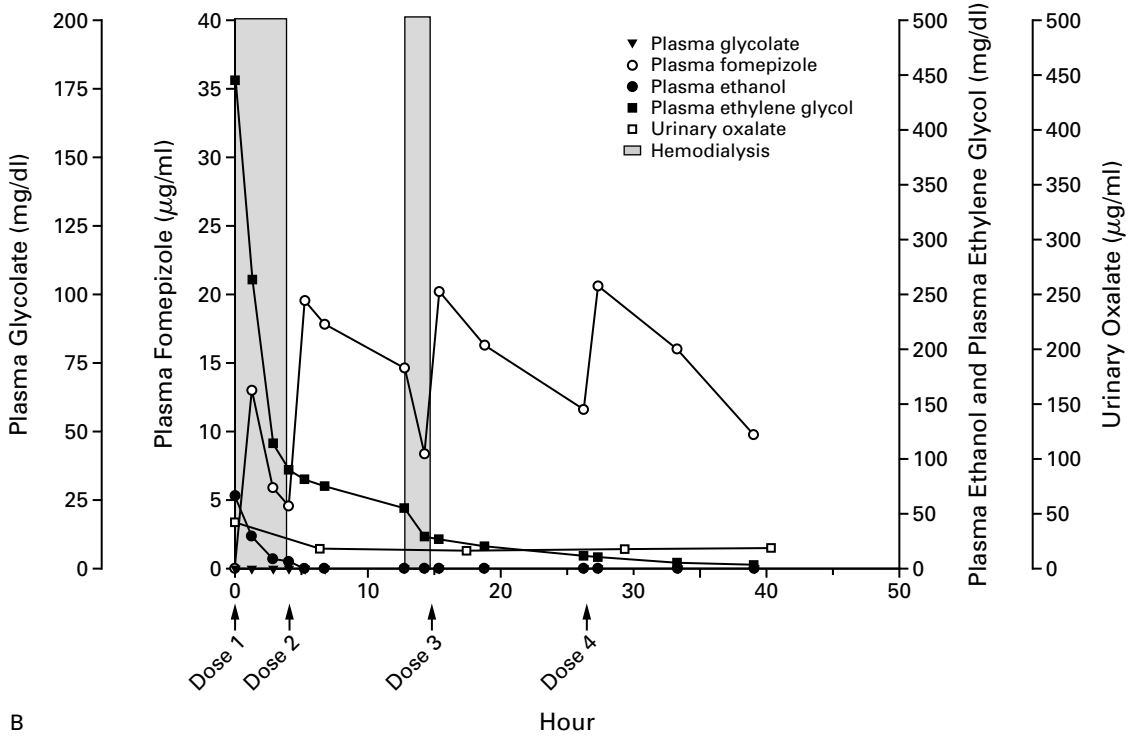

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Figure 4. Serial Plasma Glycolate, Fomepizole, Ethanol, and Ethylene Glycol Concentrations and Urinary Oxalate Excretion in Two Patients with Ethylene Glycol Poisoning.

Panel A shows the values in a 73-year-old man who presented seven hours after ingesting antifreeze in an attempt at suicide. His initial arterial pH was 7.22. He was treated with fomepizole, underwent hemodialysis for six hours, and recovered uneventfully. Panel B shows the values in a 35-year-old woman who presented six hours after ingesting antifreeze in an attempt at suicide. Her initial arterial pH was 7.42. She was treated with fomepizole, underwent hemodialysis twice (initially for four hours and subsequently for two hours), and recovered uneventfully. To convert the values for plasma ethylene glycol to millimoles per liter, multiply by 0.161. To convert the values for plasma glycolate to millimoles per liter, multiply by 0.132. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for plasma ethanol to millimoles per liter, multiply by 0.217.

Adverse Effects

No adverse effects were rated by the local investigators as either definitely or probably related to fomepizole. The only adverse effects rated as possibly related to fomepizole were bradycardia, seizure, and headache. One 35-year-old man had transient bradycardia (heart rate, 50 to 60 beats per minute) 2.5 hours after he received his first dose of fomepizole. The other episode of bradycardia (heart rate, 60 beats per minute) occurred in a 20-year-old man 16 hours after his last dose. A 57-year-old man had a generalized seizure during an evolving myocardial infarction that had begun before admission. This seizure occurred 15 minutes after his first dose of fomepizole. The second patient who had a seizure was a 33-year-old man in whom one 45-to-60-second seizure occurred 15 minutes after the administration of the first dose. This patient had no further seizures after subsequent doses. Two patients had headaches: one 16 hours after his last dose of fomepizole and one during the second day of a two-day course of therapy.

DISCUSSION

The results of this study suggest that fomepizole is a safe and effective antidote in the treatment of ethylene glycol poisoning. The plasma concentration of fomepizole that is necessary to inhibit alcohol dehydrogenase is approximately 0.8 μg per milliliter,[8,22] and this concentration was exceeded in our patients. The decreases in plasma glycolate concentrations and urinary oxalate excretion indicated that the metabolism of ethylene glycol was inhibited. The inhibition of metabolite production coincided with the resolution of metabolic acidosis, which occurred a mean of three hours after the initiation of therapy.

Renal function decreased during therapy in nine patients, all of whom had had abnormal renal function at enrollment. In contrast, the patients with normal serum creatinine concentrations at enrollment had no change in renal function. This pattern is similar to that of nine treated patients who have been described in previous reports: only the three with high serum creatinine concentrations at the start of treatment with fomepizole had further increases during treatment.[12-16]

The doses of fomepizole used in this study appeared to have few side effects. The adverse effects thought to be possibly related to fomepizole were bradycardia, seizures, and headaches, but their clinical course suggests that they were not related to fomepizole. In addition, these side effects were not described in phase 1 studies[10,11] or in the previous case reports of patients with ethylene glycol poisoning who were treated with fomepizole.[12-16] In the case reports, the adverse effects were a rash (in one patient), high serum aminotransferase concentrations (in one), and eosinophilia (in two).[12] These effects were not noted in any of our patients.

The standard treatment for ethylene glycol poisoning is ethanol, but this approach has not been studied prospectively, and little information is available on the effect of ethanol on ethylene glycol metabolism or on the rate of recovery. Because the kinetics of ethanol are unpredictable,[5,6] patients have traditionally received hemodialysis if their plasma ethylene glycol concentrations exceeded 50 mg per deciliter. All the patients in our study who had plasma ethylene glycol concentrations in excess of this value underwent hemodialysis, according to our protocol. Fomepizole-treated patients who do not have acidosis but who have higher plasma ethylene glycol concentrations than those in our patients would probably not require hemodialysis. The ratio of urinary to serum ethylene glycol concentrations is high, and the renal clearance is 17 to 70 ml per minute.[14,23,24] In the absence of metabolite production, as evidenced by an absence of acidosis, it is likely that plasma ethylene glycol concentrations in excess of 50 mg per deciliter would be well tolerated during treatment with fomepizole, as long as renal function was normal.

This study has limitations. Although the data suggest that fomepizole is effective, there was no untreated control group. Given the morbidity and mortality associated with ethylene glycol poisoning, inclusion of an untreated group was impossible. The trial was not designed to compare fomepizole with ethanol, but the results suggest that fomepizole has several advantages. Fomepizole does not affect mental status or cause hypoglycemia, and maintaining therapeutic plasma concentrations is not difficult.

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Dr. McMartin has a royalty agreement with Orphan Medical, the manufacturer of fomepizole, and serves as a consultant to the company.

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APPENDIX

Other members of the Methylpyrazole for Toxic Alcohols Study Group were G. Bogdan, R. Dart, K. Heard, L. Kokan, Denver; J. Akhtar, N. Ahsan, H. Zimmerman, Hershey, Pa.; S. Curry, K. Wallace, Phoenix; C. Aaron, M. Burns, C. Graudins, S. Hartigan, Worcester, Mass.; C. Hantsch, D. Seger, Nashville; R. Berlin, D. Douglas, Portland, Oreg.; S. White, Detroit; M. Kirk, Indianapolis; J. Hollander, Stony Brook, N.Y.; M. Ford, William Kerns, C. Tomaszewski, Charlotte, N.C.; C. McKay, Hartford, Conn.; P. Wax, Rochester, N.Y.

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