FOMEPIZOLE FOR THE TREATMENT OF METHANOL POISONING

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ABSTRACT

Background Methanol poisoning may result in metabolic acidosis, blindness, and death. The inhibition of alcohol dehydrogenase is fundamental to the treatment of methanol poisoning. We performed a multicenter study to evaluate fomepizole, an inhibitor of alcohol dehydrogenase, in the treatment of patients with methanol poisoning.

Methods We administered intravenous fomepizole to 11 consecutive patients who presented with methanol poisoning at a participating center. Serial clinical and laboratory studies, including measurements of plasma formic acid and fomepizole, were performed. The outcomes measured were the preservation of visual acuity, the resolution of metabolic acidosis, the inhibition of formic acid production, the achievement of therapeutic plasma concentrations of fomepizole with the dosing regimen, residual illness or disability, and death.

Results Plasma formic acid concentrations were detectable in eight patients, and these concentrations were closely correlated with the initial arterial pH values ($r=0.92$, $P<0.001$). In response to fomepizole, plasma formic acid concentrations fell and metabolic abnormalities resolved in all patients. Nine patients survived. Seven patients initially had visual abnormalities, but at the end of the trial no surviving patient had any detectable visual deficits related to methanol poisoning. Fomepizole had few adverse effects. The two patients who died had anoxic brain injury that was present at the time of enrollment. During treatment, methanol had an elimination half-life of 54 hours.

Conclusions Fomepizole appears to be safe and effective in the treatment of methanol poisoning. (N Engl J Med 2001;344:424-9.)

METHANOL poisoning may cause severe illness or death.[1,2] Although methanol itself is not highly toxic, it is metabolized by alcohol dehydrogenase to formaldehyde and subsequently to formic acid (Fig. 1); these metabolites cause the metabolic acidosis, blindness, cardiovascular instability, and death attributed to methanol toxicity.[2-4]

Inhibition of alcohol dehydrogenase and, in selected patients, hemodialysis are the traditional treatments for methanol poisoning.[2] At present, no inhibitors of alcohol dehydrogenase are approved by the Food and Drug Administration (FDA) for the treatment of methanol poisoning. However, the competitive substrate ethanol is commonly administered in an attempt to inhibit methanol metabolism.[2,5,6] There are problems with the therapeutic use of ethanol. Intravenous preparations are often not available, and the pharmacokinetic characteristics of ethanol are erratic, making it difficult to maintain adequate plasma concentrations.[7,8] Thus, plasma ethanol must be measured often and appropriate dose adjustments made. Furthermore, patients treated with ethanol need to be closely monitored because they are intoxicated and at risk for liver injury and hypoglycemia. In fact, there has never been a prospective study of the efficacy of ethanol in the treatment of methanol poisoning; all the clinical data are from case reports and retrospective case series.

Fomepizole (4-methylpyrazole) is an inhibitor of alcohol dehydrogenase that appears to have few of the adverse effects of ethanol.[2,9-15] Fomepizole is an effective treatment for methanol poisoning in animals[16-18] and is effective and well tolerated as a treatment for ethylene glycol poisoning.[14] We report the results of the Methylpyrazole for Toxic Alcohols Study, a clinical trial of fomepizole in the treatment of methanol poisoning.

METHODS

Study Design

Our study was a multicenter, prospective trial in which consecutive patients with methanol poisoning were enrolled between November 1995 and August 1997. Records were kept on any patient with methanol poisoning who was admitted to a participating center and was inadvertently not enrolled. The protocol was approved by the institutional review board at each participating hospital, and each patient or a surrogate gave written informed consent.

Inclusion and Exclusion Criteria

Patients who were at least 12 years old were eligible for inclusion in the study if they had a serum methanol concentration of more than 20 mg per deciliter (6.2 mmol per liter) or if there was a history or a strong suspicion of methanol ingestion, in addition to at least two of the following three findings: an arterial pH of less than 7.3, a serum bicarbonate concentration of less than 20 mmol per liter, or a serum osmolality gap (determined by the freezing-point depression) of more than 10 mOsm per kilogram of water.[14] Patients were excluded if they had received ethanol treatment,

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*Other members of the Methylpyrazole for Toxic Alcohols Study Group are listed in the Appendix.

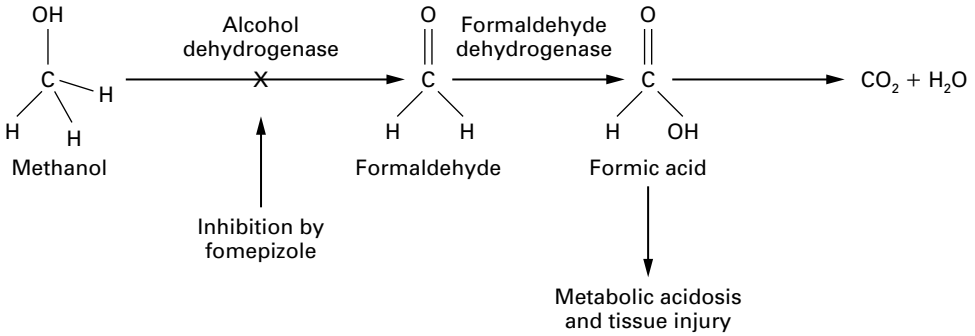

Figure 1. Metabolism of Methanol to Formic Acid.

Alcohol dehydrogenase is the primary enzyme for the oxidation of methanol to formaldehyde, and this oxidation reaction is the rate-limiting step in the metabolism of methanol. Formaldehyde dehydrogenase is the principal enzyme involved in the oxidation of formaldehyde.

had a known adverse reaction to pyrazoles, or were pregnant. Four patients who were enrolled on the basis of presumptive methanol poisoning did not have a serum methanol concentration of more than 20 mg per deciliter, as required for inclusion. These four patients received at least one dose of fomepizole and were therefore included in the analyses of adverse events and plasma fomepizole concentrations.

Treatment Protocol

The treatment protocol consisted of the administration of fomepizole, with the intravenous infusion of glucose, electrolytes, and fluids, as clinically indicated. All patients received supplemental folate. Oxygenation was maintained at a saturation level of over 90 percent, if possible. Fomepizole (Antizol, provided by Orphan Medical, Minnetonka, Minn.) was administered intravenously as a loading dose of 15 mg per kilogram of body weight, followed by bolus doses of 10 mg per kilogram every 12 hours. After 48 hours, the bolus doses were increased to 15 mg per kilogram, administered every 12 hours, to counteract the induction of fomepizole metabolism.[13]

Patients were treated with fomepizole until the serum methanol concentration was less than 20 mg per deciliter. All other aspects of the protocol were continued until 24 hours after the last dose of fomepizole had been administered.

Patients underwent hemodialysis after the administration of the loading dose of fomepizole for any of the following reasons: an initial arterial pH of less than 7.1; a decrease in the arterial pH of more than 0.05 unit or a serum bicarbonate concentration of more than 5 mmol per liter, despite bicarbonate supplementation; an arterial pH that could not be maintained at 7.3 or higher; a serum methanol concentration of more than 50 mg per deciliter (15.6 mmol per liter); any of a predetermined set of visual symptoms and signs; or a serum methanol concentration that declined at a rate of less than 10 mg per deciliter (3.1 mmol per liter) per 24 hours.

Monitoring of Patients

All patients were examined daily and underwent cardiac monitoring during the trial. Serum electrolytes, urea nitrogen, and creatinine and arterial blood gases were measured at base line and subsequently at regular intervals. Comprehensive toxicologic screening of urine was performed at the time of enrollment. Determinations of best corrected visual acuity, funduscopic examinations, complete blood counts, liver-function tests, electrocardiographic studies, and urinalyses were performed at the time of enrollment and daily during the study. Plasma methanol, formic acid, ethanol, and fomepizole were measured at base line and at predetermined intervals, ranging from 1 to 12 hours, until 24 hours after the plasma methanol concentration had fallen to a level below 20 mg per deciliter. For patients who underwent hemodialysis, plasma methanol, formic acid, and fomepizole were measured simultaneously from the arterial and venous limbs of the dialyzer, and the flow rates were recorded, at predetermined intervals ranging from two to four hours. Plasma methanol was measured at both the institution at which the patient was treated and the reference laboratory at Louisiana State University Medical Center; the values determined locally were used to guide the administration of fomepizole. The values reported here were determined at the reference laboratory.

Laboratory Methods

Plasma samples obtained for the reference laboratory were frozen immediately. Plasma methanol was measured by gas chromatography.[19] Plasma formic acid was converted to methyl formate[20] and measured by head-space gas chromatography.[21] Plasma fomepizole was measured by a modification of the method of high-performance liquid chromatography described by McMartin et al.[22] and Diczfalusy and Eklof.[23]

Adverse Events

With regard to each adverse event, the local investigators determined the dates of its onset and resolution, its severity, its relation to fomepizole, the treatment required, and the outcome.

Efficacy and Outcome Assessments

The following predetermined outcomes were assessed: preservation of visual acuity, inhibition of formic acid production, resolution of metabolic acidosis, maintenance of a plasma fomepizole concentration of more than 0.8 μg per milliliter (10 μmol per liter) with the dosing regimen, residual illness or disability, and death. The target plasma fomepizole concentration of more than 0.8 μg per milliliter was based on preclinical studies.[10] All patients were followed for at least 24 hours after the completion of treatment. If there were residual effects of methanol poisoning, the patient was followed until the effects resolved.

Statistical Analysis

Objective data were verified by a study nurse who reviewed the medical records at each site. Mean values were compared with use of Student's unpaired t-test and nominal variables with use of Fisher's exact test. Correlations were determined with the Pearson correlation coefficient.

RESULTS

The mean (±SD) age of the 11 patients was 40±13 years. Of the nine patients for whom the ingested

product was known, eight had drunk windshield-wiper fluid, and one had ingested gas-line antifreeze. For the other two patients, the source of methanol was unknown. Four patients also reported that they had ingested carisoprodol, an over-the-counter cough syrup, mouthwash, or an unidentified solvent. The only result of toxicologic testing that could explain the clinical presentation of the other five patients was methanol poisoning. Methanol was ingested to attempt suicide in six patients, to cause inebriation in two, accidentally in two, and for unknown reasons in one.

The clinical characteristics of the 11 patients at the time of admission are shown in Table 1. Three patients had initial plasma ethanol concentrations of at least 100 mg per deciliter (21.7 mmol per liter); all three had received ethanol at referring hospitals before they were enrolled in the study. There was a strong inverse correlation between the initial arterial pH values and the plasma formic acid concentration ($r=0.92$, $P<0.001$) (Fig. 2). Of the three patients who had undetectable plasma formic acid concentrations at the time of presentation, only one (Patient 1) had a high plasma ethanol concentration. For the group as a whole, there was no correlation between the initial plasma formic acid and ethanol concentrations ($P=0.96$).

Seven patients had visual abnormalities, manifested as symptoms, decreased visual acuity, or other abnormal results on examination. The mean plasma formic acid concentration in this group was 80 mg per deciliter (17.5 mmol per liter) with a range of 0 to 198 mg per deciliter (0 to 43.0 mmol per liter), as compared with 7.4 mg per deciliter (1.6 mmol per liter) with a range of 0 to 24.5 mg per deciliter (0 to 5.33 mmol per liter) in the patients with no visual abnormalities ($P=0.08$). Patients 6 and 10 had sluggish pupillary light reflexes, Patient 6 had peripapillary edema, Patient 9 had hyperemia of the optic disk, and Patients 4 and 11, who were comatose, had fixed dilated pupils. Patients 1, 2, and 6 had blurring of vision, and Patient 2 had a central scotoma. On initial presentation at the referring hospital, Patient 4 reported that he felt as if he were going blind. All patients who could be evaluated had normal extraocular movements. No patient reported diplopia, seeing spots, or the sensation of seeing through a snowstorm.

Clinical Course

The median duration of treatment with fomepizole was 30 hours (range, 0.5 to 60), and the patients received a median of 4 doses (range, 1 to 10). The seven patients who underwent hemodialysis received a median of one treatment (range, one to four). The median interval between enrollment and the initiation of hemodialysis was 90 minutes (range, 14 to 160).

After the institution of fomepizole therapy, plasma formic acid concentrations fell in all patients (Fig. 3), with simultaneous resolution of the metabolic acidosis and improvements in mental status and visual symptoms and signs. No patient had hypoglycemia after the initiation of therapy. Methanol elimination in patients who did not undergo dialysis (Fig. 3B) followed first-order kinetics, with a half-life of 54 hours.

Plasma fomepizole, measured a total of 155 times

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 11 PATIENTS WITH METHANOL POISONING.*

PATIENT NO.	AGE (YR)/SEX	MENTAL STATUS AT PRESENTATION	TIME TO TREATMENT	ARTERIAL pH	PLASMA METHANOL	PLASMA FORMIC ACID	PLASMA ETHANOL	INITIAL VISUAL ACUITY†	HEMODIALYSIS	OUTCOME
			hr		mg/dl	mmol/liter	mg/dl			
1	38/M	Awake	12.7	7.46	75.3	ND	151.2	20/100	Yes	Recovered
2	42/M	Comatose	Unknown	7.21	66.9	20.6	104.3	FC‡	Yes	Recovered
3	32/M	Somnolent	6.3	7.38	38.8	ND	10.7	U	No	Recovered
4	61/M	Comatose	>24.0	6.90	129.0	21.0	198.9	U	Yes	Recovered
5	18/M	Awake	23.5	7.34	37.4	5.33	67.8	20/20	No	Recovered
6	53/M	Lethargic	26.4	7.38	612.1	9.89	89.1	FC§	Yes	Recovered
7	34/F	Awake	3.3	7.44	36.7	0.48	ND	20/20	No	Recovered
8	35/M	Awake	3.5	7.42	23.0	0.64	ND	20/20	No	Recovered
9	51/M	Awake	23.5	7.42	300.0	ND	10.9	20/20, 20/25	Yes	Recovered
10	25/F	Comatose	Unknown	7.01	71.3	27.7	ND	U	Yes	Died
11	45/M	Comatose	Unknown	6.90	484.0	43.1	ND	U	Yes	Died

*ND denotes not detected, and U unobtainable. FC indicates that during a visual examination, the patient was able only to count fingers. To convert the values for methanol to millimoles per liter, multiply by 0.312. To convert the values for ethanol to millimoles per liter, multiply by 0.217. To convert the values for formic acid to milligrams per deciliter, multiply by 4.6.

†If not identical for both eyes, visual acuity is given as right eye/left eye.

‡Visual acuity in this patient was measured at the referring hospital, before transfer and enrollment in the study.

§This patient had only one eye.

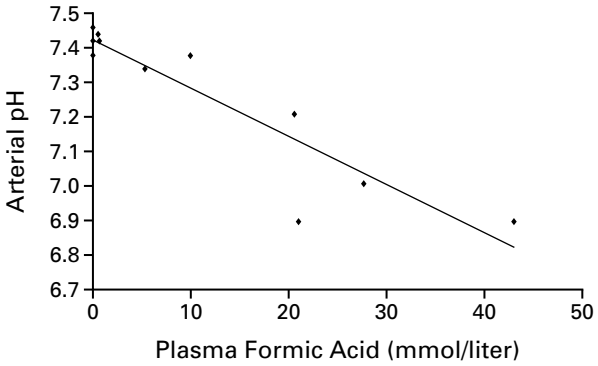

Figure 2. Initial Plasma Formic Acid Concentrations and Arterial Blood pH Values in 11 Patients with Methanol Poisoning.

Plasma formic acid and pH were measured within one hour of each other. To convert the values for formic acid to milligrams per deciliter, multiply by 4.6.

during therapy in all patients, was at or above the target concentration of 0.8 μg per milliliter on all but three occasions.

Adverse Events

Adverse events in six patients were classified by the treating physicians as possibly related to fomepizole. These were phlebitis, dyspepsia, anxiety, agitation, hiccups, a reaction at the infusion site, transient tachycardia, transient rash, and a "strange" feeling. Each of these events occurred in only one patient, except for agitation, which was reported by two patients. The rash occurred after four doses of fomepizole in Patient 9, who had a history of allergic reactions to sulfonamide drugs and who was also receiving methadone, clonidine, lorazepam, and vitamins. He received two additional doses of fomepizole, with no recurrence of the rash.

Outcome

Patients 10 and 11 died as a result of methanol poisoning. At the time of enrollment, both were comatose and had severe acidosis, and they had the highest plasma formic acid concentrations measured in this study (Table 1). Both patients died of anoxic brain injury.

At the end of the trial, no patient appeared to have any decrements in visual acuity that were related to methanol poisoning. Patients 3 and 6 had decreased corrected visual acuity. Patient 6 was a 53-year-old man with a prosthesis in one eye and known optic atrophy in his other eye, resulting from a prior episode of methanol poisoning. His base-line visual acuity was 20/200. Initially, 26.5 hours after ingesting gas-line antifreeze containing methanol, he could only count fingers. After treatment, his visual acuity was once again 20/200. Patient 3 was a 32-year-old man who had ingested carisoprodol and windshield-wiper fluid and was somnolent on presentation. He was quickly intubated, and no visual acuity measurements could be performed until the third hospital day. At that time, his visual acuity was 20/30 in his left eye, 20/200 in his right eye, and 20/50 in both eyes. He had no visual symptoms, and the results of a funduscopic examination were normal. A follow-up evaluation was not performed because he was transferred to a psychiatric hospital. He did not have metabolic acidosis, nor was formic acid detected in his plasma at the time of enrollment.

DISCUSSION

Studies in animals have suggested that fomepizole may be effective in the treatment of methanol poisoning, but clinical experience with its use in this context has been limited to three reports.[24-26] Our findings suggest that fomepizole is a safe and effective antidote for use in the treatment of methanol poisoning. The plasma concentration of fomepizole that is necessary to inhibit alcohol dehydrogenase is approximately 0.8 μg per milliliter,[10,27] and in our study, 98 percent of the measurements performed during therapy exceeded this value. Therefore, the production of formic acid from methanol should have been inhibited, and the measurements of plasma formic acid indicated that this occurred. Formic acid, which is the major circulating metabolite of methanol,[4,27,28] appears to be responsible for the effects of methanol poisoning.[29,30]

Three patients had decreased visual acuity on presentation, and vision could not be evaluated in four other patients, three of whom were severely intoxicated with methanol. The three patients with severe intoxication had the highest plasma formic acid concentrations in the study. Two of these patients died before their vision could be assessed, and the third (Patient 4) had 20/20 vision after treatment. In all patients who could be evaluated, visual acuity appeared to return to base line.

Seven patients underwent hemodialysis. In the absence of a substantial accumulation of formic acid, as indicated by the absence of acidosis, hemodialysis is useful only to remove methanol itself. We found that with therapeutic plasma concentrations of fomepizole, little methanol was metabolized. This result suggests that hemodialysis may be unnecessary in patients without acidosis who are treated with fomepizole. However, since the median plasma half-life of methanol was 54 hours in the patients who did not undergo hemodialysis, treatment with hemodialysis may be warranted to prevent prolonged hospitalization of patients with very high plasma methanol concentrations.

There were few adverse events in our study. Similarly, patients with ethylene glycol poisoning who

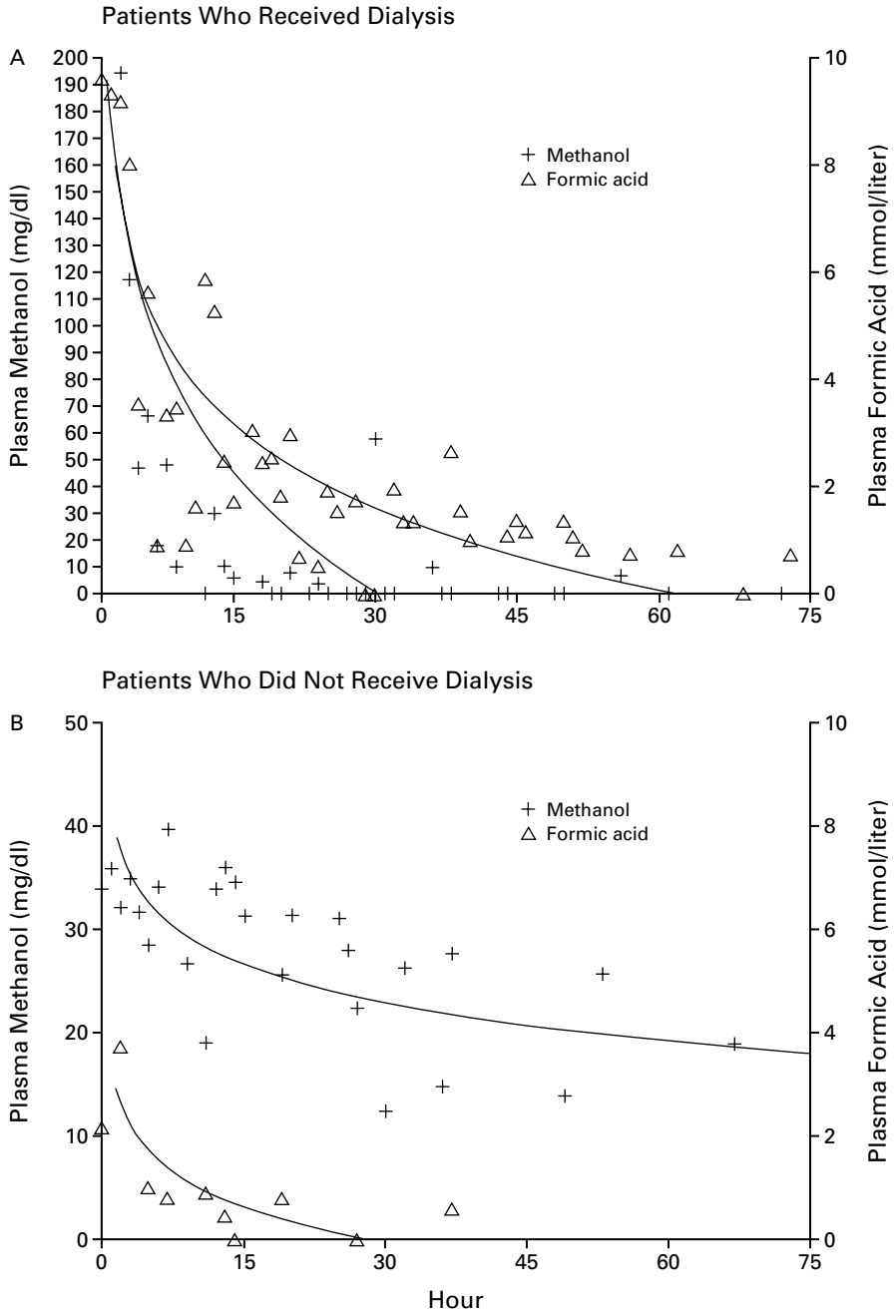

Figure 3. Mean Plasma Formic Acid and Methanol Concentrations during Fomepizole Therapy.

Panel A shows the values in five patients who underwent hemodialysis, and Panel B the values in three patients who did not. All eight patients had detectable plasma formic acid at the time of enrollment. The values at time zero were obtained within an hour after the initiation of fomepizole therapy. To convert the values for formic acid to milligrams per deciliter, multiply by 4.6. Curves indicate means, and symbols indicate individual values.

were treated with fomepizole had few adverse events.[14] In the ethylene glycol study, the only events that occurred in more than one patient were seizures, headaches, and bradycardia, none of which appeared to be related to fomepizole therapy. Case reports from France of patients treated with fomepizole have noted a rash in two patients,[15,31] high serum aminotransferase concentrations in three,[31,32] and eosinophilia in four.[15,31]

This study was not designed to compare fomepizole with ethanol. An evaluation of the therapeutic superiority of fomepizole would require hundreds of patients. Given the rarity of methanol poisoning, such a trial is unfeasible. However, our results suggest that fomepizole may have advantages over ethanol in the treatment of methanol poisoning. Unlike ethanol, fomepizole does not require separate preparation or compounding. Therapeutic plasma concentrations are reliably achieved with the dosing regimen used in this study. No changes in mental status, hepatotoxicity, or hypoglycemia occurred with the use of fomepizole. Although there is considerable anecdotal experience with the use of ethanol, there are few data on methanol metabolism or rates of recovery from methanol poisoning in patients treated with ethanol. We conclude that fomepizole appears to be a safe and effective treatment for patients with methanol poisoning.

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Dr. Brent has served on the Speakers' Bureau of Orphan Medical, the manufacturer of fomepizole, and Dr. McMartin has a royalty agreement with Orphan Medical and has served as a consultant to the company.

APPENDIX

In addition to the authors, the Methylpyrazole for Toxic Alcohols Study Group consisted of the following investigators: Denver — G. Bogdan, R. Dart, K. Heard, M. Wells; Phoenix, Ariz. — S. Curry, K. Wallace; Worcester, Mass. — M. Burns, A. Graudins, C. Hartigan, M. Sivilotti; Nashville — C. Hantsch, D. Seger; Portland, Oreg. — R. Berlin, D. Douglas; Detroit — S. White; Indianapolis — M. Kirk; Stony Brook, N.Y. — J. Hollander; Charlotte, N.C. — M. Ford, W. Kerns, C. Tomaszewski; Hartford, Conn. — C. McKay; Rochester, N.Y. — P. Wax.

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