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ORIGINAL

Treatment of acute methanol poisoning with fomepizole

Bruno Mégarbane
Stephen W. Borron
Hervé Trout
Philippe Hantson
Albert Jaeger
Eliane Krencker
Chantal Bismuth
Frédéric J. Baud

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B. Mégarbane (✉) · S. W. Borron · C. Bismuth · F. J. Baud
Réanimation Médicale et Toxicologique, Hôpital Lariboisière, Université Paris VII, 2, rue Ambroise Paré, 75475 Paris CEDEX 10, France
E-mail: bruno-megarbane@wanadoo.fr
Phone: +33-1-49 95 64 91
Fax: +33-1-49 95 65 78

B. Mégarbane · S. W. Borron · F. J. Baud
INSERM U 26, Hôpital Fernand Widal, 200, rue du Faubourg-St-Denis, 75475 Paris CEDEX 10, France

H. Trout
Pharmacie, Hôpital Lariboisière, Université Paris VII, 2, rue Ambroise Paré, 75475 Paris CEDEX 10, France

P. Hantson
Unité de Toxicologie, Service des Soins Intensifs, Cliniques Universitaires St-Luc, 10, Avenue Hippocrate, UCL 10/27.02, 1200 Brussels, Belgium

A. Jaeger
Réanimation Médicale, Hôpitaux Universitaires, 1 Place de l'Hôpital, 67000 Strasbourg, France

E. Krencker
Centre antipoison, Hôpitaux Universitaires, 1 Place de l'Hôpital, 67000 Strasbourg, France

S. W. Borron
Department of Emergency Medicine, George Washington University School of Medicine, 2140 Pennsylvania Ave. NW, Washington, DC 20037 USA

Abstract *Objective:* To assess the efficacy and safety of fomepizole, a competitive alcohol dehydrogenase inhibitor, in methanol poisoning and to test the hypothesis that fomepizole obviates the need for hemodialysis in selected patients.
Design and setting: Retrospective clinical study in three intensive care units in university-affiliated teaching hospitals.
Patients: All methanol-poisoned patients admitted to these ICUs and treated with fomepizole from 1987–1999 (n = 14).
Measurements and results: The median plasma methanol concentration was 50 mg/dl (range 4–146), anion gap 22.1 mmol/l (11.8–42.2), arterial pH 7.34 (7.11–7.51), and bicarbonate 17.5 mmol/l (3.0–25.0). Patients received oral or intravenous fomepizole until blood methanol was undetectable. The median cumulative dose was 1250 mg (500–6000); the median number of twice daily doses was 2 (1–16). Four patients underwent hemodialysis for visual impairment present on admission. Four patients with plasma methanol concentrations of 50 mg/dl or higher and treated without hemodialysis recovered fully. Patients without pretreatment visual disturbances recovered, with no sequelae in any case. There were no deaths. Fomepizole was safe and well tolerated, even in the case of prolonged treatment. Analysis of methanol toxicokinetics in five patients demonstrated that fomepizole was effective in blocking methanol's toxic metabolism.
Conclusions: Fomepizole appears safe and effective in the treatment of methanol-poisoned patients. If our results are confirmed in prospective analyses, hemodialysis may prove unnecessary in patients presenting without visual impairment or severe acidosis.

Keywords Acute intoxication · Efficacy · Fomepizole · Hemodialysis · Methanol · Safety

Introduction

Acute methanol poisoning, while relatively uncommon, remains an important cause of epidemics, resulting in countless deaths and serious sequelae [1, 2, 3]. Since 1998 alone, methanol has been responsible for at least 300 deaths in Eastern Europe, Africa, and Asia (BBC News: "Vietnamese killed in Cambodian revenge attacks," 4 September 1998; "Kenyan alcohol deaths," 26 August 1998; "Nine die from drinking poisonous brandy in Serbia," 4 February 1998; http://news.bbc.co.uk). This intoxication is characterized by severe metabolic acidosis, central nervous system depression and blindness [4]. Toxicity is due to the enzymatic degradation of methanol, by alcohol dehydrogenase (ADH) to formaldehyde, then by aldehyde dehydrogenase to formate [5, 6]. Inhibition of metabolism renders methanol relatively nontoxic [6, 7].

The classic treatment of methanol poisoning includes ethanol, a competitive substrate of ADH, and hemodialysis [4, 7]. Sodium bicarbonate is used in severe acidosis, and folinic acid may inhibit ocular toxicity by stimulating conversion of formate to CO_2 and H_2O [8, 9]. Fomepizole (4-methylpyrazole), a potent ADH inhibitor [10], has been successfully used in the treatment of ethylene glycol poisoning in humans [11, 12, 13]. It is also effective in preventing methanol toxicity in animals [10, 14]. A few methanol-poisoned patients have been treated with fomepizole [15, 16, 17], and the North American prospective clinical trial yielded recently very promising results [18, 19, 20, 21].

In ethylene glycol poisoning, patients treated with fomepizole before onset of significant acidosis or renal failure often do not require hemodialysis [13]. We hypothesized that fomepizole obviates the need for hemodialysis in selected methanol-poisoned patients. We thus conducted a multicenter retrospective review to assess fomepizole's efficacy and safety in the treatment of methanol-poisoned patients and their requirements for hemodialysis.

Materials and methods

Patient characteristics and data collection

We retrospectively reviewed intensive care admissions to three university hospitals from 1987 to 1999 for patients with documented methanol exposure given at least one dose of fomepizole. Demographics, clinical and laboratory parameters, and outcome were collected using standardized case report forms based on information available in the medical chart. The study included 14 patients: nine men, five women; median age 46 years, range (Table 1). Two cases (patients 2 and 8) have been previously reported [16]. The ingested products were cooking alcohol ($n = 7$), pure methanol ($n = 4$), windshield washing fluid (25% methanol, 9% isopropanol; $n = 1$), or undetermined ($n = 2$). Patient 14 coingested mineral spirits. There was a history of alcoholism in 12 cases. Reasons for ingestion included suicide ($n = 10$), unintentional misuse ($n = 2$), and undetermined ($n = 2$). The median delay between intoxication and ICU admission was 13 h (3–48).

On admission nine patients were awake, one inebriated, two lethargic, and two comatose (Glasgow Coma Scores: 6 and 7). The two latter patients required mechanical ventilation (Table 2). Three patients presented with bilateral blindness and one with color vision impairment due to ophthalmological examination to optic nerve damage. Two patients complained of abdominal pain and one of vomiting, and one had rash before fomepizole treatment. On initial physical examination the median systolic blood

Table 1 Demographics and history of intoxication in 14 methanol poisoned patients (*ND* not determined)

Patient no.	Sex	Age (years)	Product ingested, amount	Reason	Ethanol ingestion
1	M	28	Windshield washing fluid (25% methanol, 9% isopropanol), 500 ml	Intentional for self-harm	No
2	M	56	ND	ND	Yes
3	M	58	ND	ND	Yes
4	M	53	Pure methanol	Accidental	No
5	M	56	Pure methanol, 20 ml	Intentional for self-harm	No
6	M	32	Cooking alcohol, 250 ml	Intentional for self-harm	No
7	M	46	Cooking alcohol, 500 ml	Intentional for self-harm	Yes
8	F	18	Pure methanol, 50 ml	Intentional for self-harm	No
9	M	45	Cooking alcohol, 250 ml and mineral spirits, 250 ml	Intentional for self-harm	Yes
10	M	54	Cooking alcohol	Intentional for self-harm	Yes
11	F	19	Cooking alcohol, 500 ml	Intentional for self-harm	Yes
12	F	41	Pure methanol, 45 ml	Accidental	No
13	F	40	Cooking alcohol, 250 ml	Intentional for self-harm	Yes
14	F	51	Cooking alcohol, 250 ml	Intentional for self-harm	Yes

Table 2 Clinical characteristics and laboratory assessments of 14 methanol-poisoned patients treated with fomepizole. Patient 2 had alcoholic ketosis, with marked elevation in urine ketones and mildly elevated plasma lactate. He had received sodium bicarbonate therapy prior to blood gas analysis. Patient 9 had plasma methanol at 23 mg/dl, when he was ethanol free (*ND* not determined)

Patient no.	Mental status	Visual impairment	Plasma methanol (mg/dl)	Prefomepizole plasma ethanol (mg/dl)	Arterial pH	Serum bicarbonate (mmol/l)	Anion gap (mmol/l)	Serum creatinine (μmol/l)
1	Inebriated	–	146	0	7.42	23.0	15.3	96
2	Lethargic	–	106	90	7.51	16.6	42.2	128
3	Awake	–	102	120	7.43	25.0	18.3	53
4	Awake	Bilateral blindness	92	0	7.21	5.4	35.3	84
5	Awake	Color vision disorder	78	129	7.16	17.0	23.1	89
6	Awake	Bilateral blindness	53	0	7.11	3.0	28.7	95
7	Comatose	–	51	28	7.29	22.0	17.0	66
8	Awake	–	49	0	7.19	10.0	28.0	94
9	Comatose	–	36	530	7.34	17.0	23.9	53
10	Awake	Bilateral blindness	12	14	7.26	7.2	33.8	83
11	Awake	–	12	12	7.42	21.0	18.1	50
12	Awake	–	10	0	ND[a]	25.0	11.8	90
13	Somnolent	–	6	270	7.35	18.0	21.0	74
14	Inebriated	–	4	35	7.41	23.9	21.1	53

pressure was 130 mmHg (range 95–154) and the diastolic blood pressure 77 mmHg (60–100). Only one patient suffering hypotension (systolic blood pressure < 95 mmHg). Median heart rate was 87/min (74–116), and three patients had tachycardia (pulse rate > 100/min). The median respiratory rate was 18/min (14–40), with six patients presenting tachypnea (respiratory rate > 20/min). One patient had cutaneous pressure lesions related to coma. One patient underwent gastric lavage, and three received activated charcoal prior to intensive care unit admission.

The median initial plasma methanol concentration was 50 mg/dl (4–146; Table 2). Eight patients coingested ethanol with a median initial plasma concentration of 195 mg/dl (12–530); three patients (5, 8, 10) received ethanol as initial therapy. In one case ethanol was administered prior to transfer of a patient to the hospital where fomepizole was administered. In the two other cases fomepizole therapy was instituted on the basis of complications. One patient developed stupor during ethanol therapy, and the other developed acute pancreatitis (probably due to methanol). The blood ethanol concentrations in these patients are noted in Table 2. Ethanol was undetectable in the other patients. No patient had a toxic screen positive for psychotropic medications or ethylene glycol. Median arterial pH was 7.34 (7.11–7.51), serum bicarbonate 17.5 mmol/l (3.0–25.0), anion gap 22.1 mmol/l (11.8–42.2), $PaCO_2$ 32 torr (8–54), PaO_2 107 torr (70–148), arterial lactate 2.2 mmol/l (0.7–6.9), and serum creatinine 84 μmol/l (50–128). Patient 8 had an initial plasma isopropanol concentration of 39 mg/dl.

Treatment with fomepizole was started based on clinical suspicion of methanol exposure before blood methanol concentrations were measured. Visual acuity was assessed daily until discharge by treating physicians and ophthalmological consultation obtained as indicated by positive findings or visual complaints. The clinical severity of methanol poisoning was assessed on admission using the Poisoning Severity Score [22]. Patient toxicity was classified as none, minor, moderate, severe, or fatal. Results of routine toxicological screens, consisting of blood ethanol, blood methanol, serum ethylene glycol, and blood, and/or urine psychotropes (benzodiazepines, carbamates, opiates, cyclic antidepressants, barbiturates, and phenothiazines) were recorded. Patients were classified according to requirement for dialysis and whether ethanol was self-administered or prescribed, rendering four groups at fomepizole administration (Fig. 1).

Determination of serum methanol

Methanol was measured by gas chromatography. The detection threshold was 5 mg/dl, with a coefficient of variation that ranged from 5% to 7%, depending on the laboratory.

Fomepizole preparation and infusion

Fomepizole was supplied either as an isotonic, nonpyrogenic, sterile, preservative-free solution (5 mg/ml; all patients except 5 and 8) or prepared by the hospital pharmacist (patients 5 and 8) from reagent grade 4-methylpyrazole after approval by the institutional ethics committee. Fomepizole was administered orally or intravenously (Table 3). The intravenous form was diluted in 250 ml sodium chloride and infused over 45 min by an infusion pump. Fomepizole dosing varied by practitioner but was generally administered twice daily. Typically a loading dose of 15 mg/kg was followed by doses of 10 mg/kg every 12 h until plasma methanol became undetectable. The method of dosing was initially based on the monkey data reported by McMartin et al. [23] and which has proven successful in humans [12].

Determination of blood methanol toxicokinetics during fomepizole

In cases in which a sufficient number of plasma methanol concentrations were determined, toxicokinetic parameters were comput-

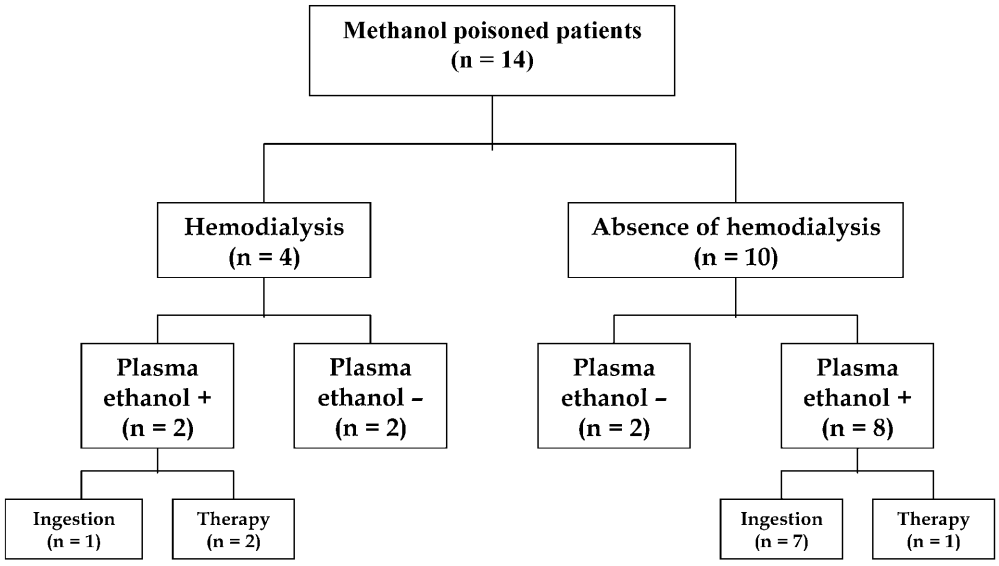

Fig. 1 Classification of methanol-poisoned patients according to treatment with hemodialysis, presence of ethanol in plasma and source of plasma ethanol. One patient both ingested and was treated with ethanol

ed using Kinetica software (InnaPhase, Philadelphia, Pa., USA). Only methanol concentrations obtained following the institution of fomepizole therapy were retained. When patients ingested or received ethanol therapy, toxicokinetic data were retained only after blood ethanol was no longer detectable. The toxicokinetics of hemodialysed patients were evaluated only after dialysis was terminated. We employed a one-dose intravenous bolus administration, one-compartment model. Because reliable data for the quantity of methanol consumed are unavailable, neither the apparent volume of distribution, the area under the concentration-time curves, nor the total body clearance could be calculated. Thus, only elimination half-life values are provided. The choice of the PK model (i.e., one- versus two-compartment model) was based on examination of a log-linear graph of data. We estimated the blood kinetics of methanol under fomepizole as first-order monocompartmental kinetics [19], assuming the apparent volume of distribution (V_d) of methanol to be 0.7 l/kg body weight [6]. We assumed that fomepizole does not modify V_d and calculated methanol total clearance (Clt) as follows: $Clt = (V_d \times 0.693)/t_{1/2}$. We studied the linear regression of methanol elimination half-lives and plasma methanol concentrations using the GraphPad Prism (GraphPad Software, San Diego, Calif., USA).

Statistical analysis

Demographic, diagnostic, efficacy, and safety data are described by percentages for qualitative variables and median (range) for quantitative variables. The two subgroups of patients (with/without hemodialysis) were compared using the Mann-Whitney test, with the significance level set at $p = 0.05$. Statistical analysis was performed using Statview software (Abacus Concepts, Berkeley, Calif., USA).

Results

Analysis of fomepizole efficacy in methanol poisoning

According to the Poisoning Severity Score [22], five patients had severe, four moderate, two minor, and three no signs or symptoms related to their intoxication. Ten patients were treated with intravenous and four with oral fomepizole, with a median loading dose of 675 mg (500–1200), i.e., approx. 10.8 mg/kg (7.8–16.3). A median of 2 (1–16) doses was necessary before plasma methanol concentrations became undetectable, patients having plasma methanol concentration greater than 50 mg/dl receiving a median of 4 (1–16) doses. The median cumulative delivered dose was 1250 mg (500–6000), i.e., approx. 20.2 mg/kg (8.3–88.2). Hemodialysis was performed only in the four patients with visual disturbances. Ethanol was prescribed in three cases on admission and was stopped within 12 h, in each case due to significant side effects (agitation and alteration of consciousness) despite close monitoring of ethanol blood levels. Two patients received sodium bicarbonate, seven folinic acid, and eight thiamine and pyridoxine. Patient 8 underwent delayed peritoneal dialysis for acute alcoholic pancreatitis present on admission. This treatment was begun 28 h after initiation of fomepizole therapy. The serum methanol concentration at that time was below 20 mg/dl and the patient had already received three doses of fomepizole.

Except for patients with visual disturbances, all patients recovered without sequelae. Visual disturbances improved in only one blind patient, who several weeks after discharge could count fingers. The median ICU stay was 5 days (2–20).

The six nonhemodialysed patients with plasma methanol less than 50 mg/dl had uneventful hospital courses. Despite significant acidosis, patient 8 was not hemodialysed, due to severe agitation and combativeness, with the risks of sedation and neuromuscular blockade being judged to outweigh the need for dialysis. Four patients (1, 2, 3, and 7) with methanol concentrations of at least 50 mg/dl were not hemodialysed and recovered completely.

Table 3 Administration schedule of fomepizole. Patients were classified according to whether hemodialysis *(HD)* was employed, whether ethanol was self-administered *(ES)* or administered by the treating physicians *(ERX)*. Total doses were administered every 12 h orally or by intravenous infusion over 45 min until plasma methanol concentrations became undetectable

Patient no.	Patient classification			Route of fomepizole administration	Fomepizoleloading dose (mg/kg)	Fomepizole total dose (mg)	Number of doses	Adverse experiences	Concomitant medications	Outcome
	HD	ES	ERX							
1	–	–	–	i.v.	10	5025	16	Lymphangitis, mild eosinophilia	Gastric lavage, vitamins B_1B_6, folinic acid	Alive without sequelae
2	–	+	–	i.v.	15	2000	3	–	B_1B_6 vitamins, meprobamate	Alive without sequelae
3	–	+	–	p.o.	15	1300	2	–	Charcoal, vitamins B_1B_6, oxazepam	Alive without sequelae
4	+ (4 h)	–	–	i.v.	15	4000	4	–	Folinic acid	Bilateral blindness
5	+ (4 h)	–	+	p.o.	15	6000	6	–	Folinic acid, ethanol (119 g)	Alive with visual disturbances
6	+ (4 h)	–	–	iv	15	1000	1	–	Vitamins B_1B_6, corticoids	Bilateral blindness
7	–	+	–	i.v.	10	4000	5	Fever	Charcoal, vitamins B_1B_6, mechanical ventilation, hydroxyzine, midazolam	Alive without sequelae
8	–	–	+	p.o.	15	1800	4	–	Folinic acid, ethanol (37 g), peritoneal dialysis (48 h)	Alive without sequelae
9	–	+	–	i.v.	10	1200	2	–	Vitamins B_1B_6, midazolam, fentanyl, ranitidine	Alive without sequelae
10	+ (6.5 h)	+	+	i.v.	10	500	1	–	Vitamins B_1B_6, folinic acid, meprobamate, ethanol (30 g)	Bilateral blindness
11	–	+	–	i.v.	10	600	1	–	–	Alive without sequelae
12	–	–	–	p.o.	10	825	2	Nausea, headaches, fever	Folinic acid	Alive without sequelae
13	–	+	–	i.v.	15	1200	2	–	–	Alive without sequelae
14	–	+	–	i.v.	10	500	1	–	Charcoal, vitamins B_1B_6, folinic acid	Alive without sequelae

On inclusion 8 patients had subnormal arterial pH and 11 subnormal bicarbonate, which returned to normal with fomepizole therapy within 6 h (5–12) and 21 h (4–34), respectively, without recurrence after drug cessation. Eleven patients had elevated anion gaps, which returned to normal within 26 h (3–62).

Analysis of hemodialysis indications in methanol poisoning

Hemodialysed patients ($n = 4$) had significantly lower pH ($p = 0.01$), lower serum bicarbonate ($p = 0.01$), and larger anion gaps ($p = 0.05$) despite insignificant differences in plasma methanol concentration than non-

Table 4 Comparison between the two subgroups of patients (with or without hemodialysis), using Mann-Whitney tests

Parameter	Patients treated only with fomepizole (n = 10)	Patients treated with fomepizole + hemodialysis (n = 4)	p
Age (years)	43 (18–58)	54 (32–56)	0.3
pH	7.41 (7.19–7.51)	7.19 (7.11–7.26)	0.01
Serum bicarbonate (mmol/l)	21.5 (10.0–25.0)	6.3 (3.0–17.0)	0.01
Anion gap (mmol/l)	19.7 (11.8–42.2)	31.3 (23.1–35.3)	0.05
Plasma methanol (mg/dl)	49 (4–146)	66 (12–92)	0.5
Serum creatinine (μmol/l)	70 (50–128)	87 (83–95)	0.4
Fomepizole cumulative dose (mg)	1250 (500–5025)	2500 (500–6000)	0.8
Number of fomepizole doses	2 (1–16)	3 (1–6)	0.8

hemodialyzed patients (Table 4). These differences suggest a delay in seeking treatment, which likely contributed to their visual impairment. Neither fomepizole nor hemodialysis improved visual impairment.

Analysis of fomepizole safety in methanol poisoning

Most patients received between 1 and 4 doses of fomepizole. However, three patients received 5, 6, and 16 doses of fomepizole, representing total doses of 4000, 6000, and 5025 mg (57.1, 88.2, and 75.0 mg/kg), respectively. Despite these relatively high cumulative doses, adverse events were rare. Nausea and headache occurred in one patient, lymphangitis, a burning skin sensation, and mild transient eosinophilia in the patient receiving 16 doses, and fever was observed in two patients (one of whom received 5 doses). During fomepizole treatment prothrombin time, liver function tests, creatine phosphokinase, and platelet and white blood cell counts remained stable, suggesting acceptable fomepizole tolerance in this small group of patients.

Analysis of blood methanol toxicokinetic profiles

Toxicokinetic analyses of plasma methanol were performed in five patients (Fig. 2). During fomepizole treatment the plasma methanol elimination was linear when plotted semi-logarithmically, consistent with first-order kinetics. The median elimination half-life of plasma methanol during fomepizole therapy was 22.9 h (15.9–56.5), and the median total clearance was 17.6 ml/min (10.5–34.6). Linear regression between methanol elimination half-life and plasma methanol concentration measured from the beginning of fomepizole treatment in the absence of ethanol, was highly significant ($R^2 = 0.98$, $p = 0.0009$; Fig. 3).

Discussion

There is convincing experimental evidence of the efficacy of fomepizole in methanol poisoning [14, 23]. Formic acid, a methanol metabolite, is responsible for the early acidosis, as well as the ocular toxicity induced by inhibition of retinal and optic nerve cytochrome oxidase [5, 7, 14]. Inhibition of formate accumulation is critical in the treatment of methanol poisoning, as shown in monkeys [11] and confirmed in humans [24]. Prevention of both ocular toxicity and accumulation of formate are accomplished by administration of fomepizole in intoxicated monkeys [14]. Only a small number of human methanol poisonings have been treated with fomepizole [15, 16, 17, 18, 19, 20, 21]. At least nine of these patients underwent hemodialysis [16, 18, 19, 20] and three had associated ethanol therapy [15, 16].

We report 14 cases of methanol intoxication documented by clinical findings and confirmed by plasma methanol concentrations. Fomepizole efficiently blocked methanol metabolism, as demonstrated by alteration in toxicokinetics of methanol. In untreated overdose, methanol follows zero-order kinetics, about 8.5 mg/dl being eliminated each hour [25]. In subtoxic doses, methanol elimination apparently follows first-order kinetics, with a half-life in the range of 1.4–3.3 h [26]. Under ethanol monotherapy, methanol's half-life is about 43 h [27]. In patients treated with fomepizole, methanol elimination has been described as first order, with a slow rate of serum decline. Sivilotti et al. [20] reported a half-life of 54 h during fomepizole therapy and 10.5 h as fomepizole concentrations fell below 10 μmol/l, while Burns et al. [15] calculated an elimination half-life of 70 h. Ethanol may decrease the rate of fomepizole elimination [9]; however, one study found no significant modification of methanol's half-life under fomepizole in the presence of ethanol [20]. Moreover, ethanol clearance does not appear to be influenced by fomepizole [28].

While our treatment guidelines recommend a loading dose of 15 mg/kg, the delivered median loading dose was 12.5 mg/kg. We studied methanol toxicokinetics in five patients, in the absence of blood ethanol or

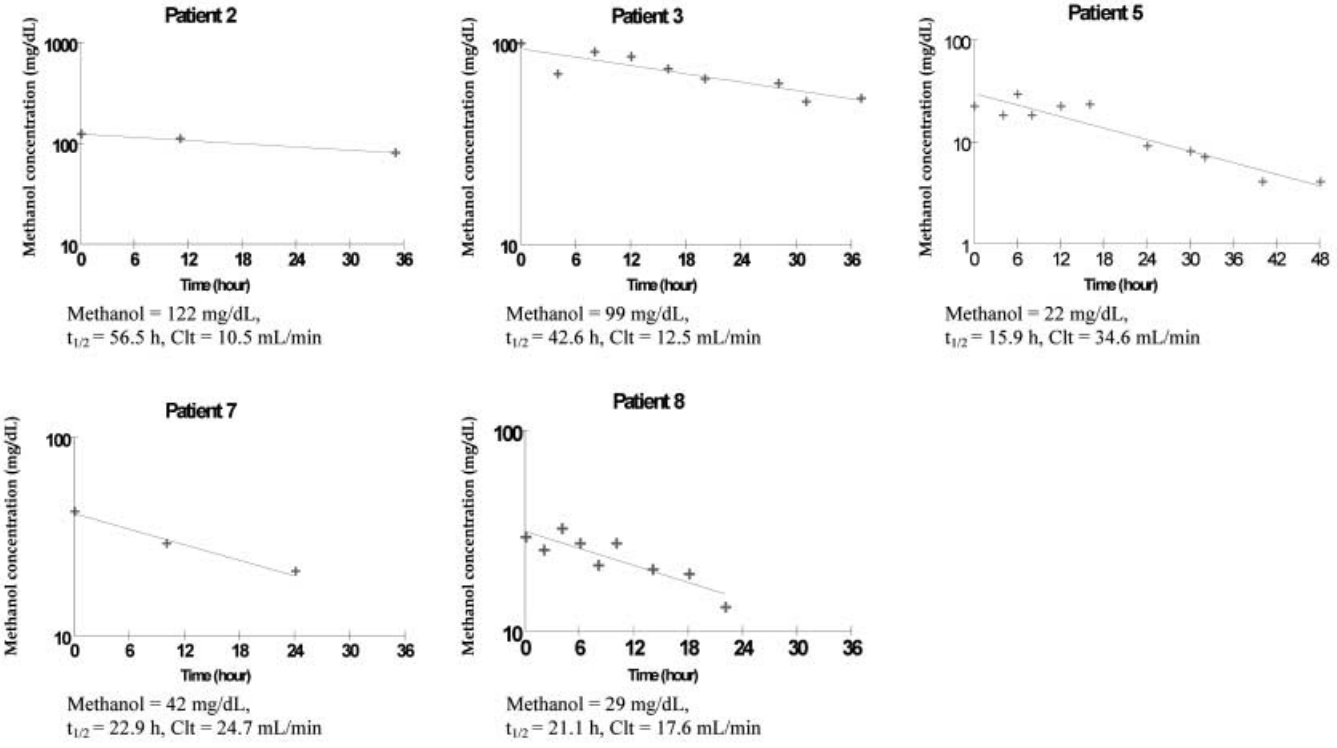

Fig. 2 Toxicokinetics of methanol in plasma during treatment with fomepizole in five poisoned patients. Plasma methanol concentration before fomepizole (mg/dl), methanol half-life ($t_{1/2}$, h), and methanol total clearance (*Clt*, ml/min) were determined for each patient. To convert methanol values to millimoles per liter, multiply by 0.312

other alcohols, and not during hemodialysis. Methanol was eliminated following first-order kinetics, with an elimination half-life of 22.9 h (15.9–56.5). Surprisingly, the analysis of the correlation between initial blood methanol concentration and elimination half-life showed a positive correlation. We cannot rule out the possibility that ADH was incompletely blocked in some patients, which could also explain the discrepancy of half-life in our patients. However, the patient with the shortest half-life received the highest doses, while the patient with the longest half-life received the lowest doses. These data suggest that the renal and pulmonary elimination of methanol is concentration dependent when ADH is completely blocked. Furthermore, in two of our patients there were only three data points, limiting the accuracy of the toxicokinetic results. The reduction or elimination of formate formation is perhaps the best indicator of efficacy of a methanol antidote. Unfortunately, blood formate concentrations were not determined in most of our patients. We used the anion gap as a surrogate marker of blood formate concentrations, given their close correlation [11, 24, 29]. Nonetheless, we believe the prolonged elimination half-life of methanol, rapid resolution of acidosis, and absence of any new signs or symptoms of methanol poisoning after initiation of fomepizole strongly suggest its efficacy in our patients. No deaths were observed, while improvements in level of consciousness and metabolic acidosis were recorded among affected patients. No sequelae were noted on discharge, except among the four patients with initial visual impairment. It is conceivable that eye fundus abnormalities were not detected in some patients due to inconsistent ophthalmology referrals. It is thus possible that some patients who might have benefited from dialysis were overlooked.

Fomepizole was well tolerated, in spite of prolonged administration (up to 8 days) in three patients. Jacobsen and colleagues [30] have shown that fomepizole is well tolerated in healthy human subjects in therapeutic doses, with no significant changes in clinical or laboratory, including liver function tests.

Fomepizole presents numerous advantages over classic ethanol treatment. Fomepizole is an inhibitor of ADH rather than a substrate, obviating the need for blood concentration monitoring, indispensable with ethanol treatment. Additionally, fomepizole causes neither CNS depression nor hypoglycemia [11, 12, 13], both of which are problematic in ethanol-treated patients [27]. Fomepizole is significantly more expensive than ethanol, but cost-benefit analysis must take into account the duration of hospitalization and need for (and risks of) hemodialysis. The cost of monitoring blood

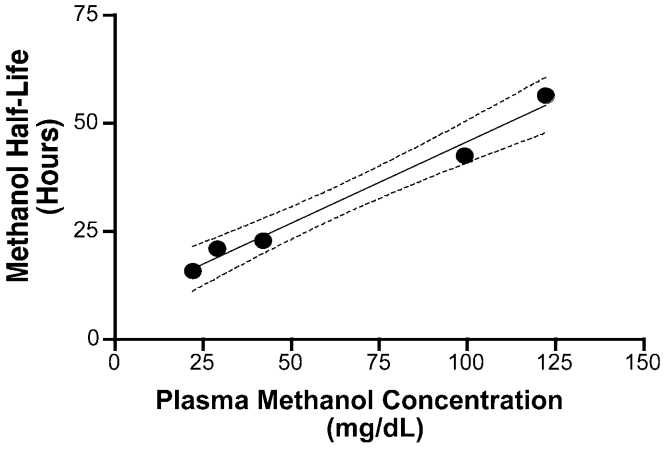

Fig. 3 linear regression between methanol elimination half-life and prefomepizole plasma methanol concentration in five poisoned patients. To convert methanol values to millimoles per liter, multiply by 0.312

ethanol concentrations repeatedly and need for frequent nursing interventions must also be considered.

Hemodialysis removes methanol from plasma [31, 32, 33, 34] but is not universally available and represents an invasive technique with risks [34]. Hemodialysis reduces the duration of acidosis in methanol poisoning [9, 34] but does not modify formate kinetics (elimination half-life) [21]. Dialysis is generally recommended in methanol poisoning in cases of visual impairment, plasma methanol concentrations exceeding 50 [7] or 60 mg/dl [6] or with severe acidosis (anion gap > 30 mmol/l or base deficit > 15 mmol/l) [6].

In our study four patients (patients 1, 2, 3, and 7) with methanol concentrations exceeding 50 mg/dl recovered completely without hemodialysis. This suggests that in poisonings involving high methanol concentrations without severe acidosis or visual impairment, patients may be successfully treated by administration of repeated doses of fomepizole without dialysis. This finding must be viewed as preliminary. If confirmed in prospective trials, fomepizole may be extremely useful in epidemic poisonings by toxic alcohols and glycols, which often occur in underdeveloped areas without analytical equipment for ethanol monitoring or access to hemodialysis. Visual impairment is traditionally considered an absolute recommendation for hemodialysis [7, 9]. However, the basis for this recommendation appears to be called in question by a recent study [18] which suggests that fomepizole arrests methanol metabolism and thus formate production, and that hemodialysis does not change formate half-life [21]. When dialysis is employed, a continuous intravenous infusion of 1–1.5 mg/kg fomepizole per hour should be administered to compensate its loss in the dialysate [35].

The prognosis of methanol poisoning is negatively correlated with coma and severe metabolic acidosis on presentation [36]. Our study included only two comatose patients, involving the ingestion of both methanol and ethanol. They recovered completely without hemodialysis. However, it should be noted that metabolic acidosis in our series was most severe among patients undergoing hemodialysis, suggesting that these patients were more severely intoxicated. Therefore our findings must await confirmation before definitive recommendations can be made regarding the need for hemodialysis in methanol poisoning.

Visual impairment, representing optic nerve injury in methanol-poisoned patients [37], remains difficult to reverse, regardless of the methanol antidote used, even in combination with hemodialysis; only one of four patients with ocular impairment in our series had objective visual improvement. Sivilotti and colleagues [19] recently reported possible reversal of early optic nerve toxicity by a combination of fomepizole and hemodialysis. Evaluation of the efficacy of this combination requires additional study.

Fomepizole appears perhaps as effective in methanol poisoning as it is in ethylene glycol poisoning [11, 12, 13]. If fomepizole proves to be reliable in preventing acidosis and visual disturbances in prospective studies involving greater numbers of patients, this would provide additional therapeutic options to centers without access to hemodialysis facilities and offer choices to institutions which do have such facilities. However, the prolonged half-life of methanol treated with fomepizole in the absence of hemodialysis may prolong hospitalization (awaiting nontoxic blood methanol concentrations). The role of hemodialysis in cases without metabolic acidosis, visual impairment, or a blood concentration exceeding 50 mg/dl may be less apparent.

In summary, fomepizole appears safe and effective in preventing or diminishing methanol toxicity in poisoned patients. Administration of fomepizole therapy is less cumbersome than that of ethanol, with few side effects. While antidotal therapy without hemodialysis appeared efficacious in a number of our cases, further experience is needed to define the requirement for hemodialysis.

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