

Bruno Mégarbane
Stephen W. Borron
Frédéric J. Baud

Current recommendations for treatment of severe toxic alcohol poisonings

Received: 2 July 2004
Accepted: 8 November 2004
Published online: 31 December 2004
© Springer-Verlag 2004

International congress presentation: presented in part at the 23rd Congress of The European Association of Poisons Centers and Clinical Toxicologists, Rome, Italy, June 2003

B. Mégarbane (✉) · F. J. Baud
Réanimation Médicale et Toxicologique,
Hôpital Lariboisière,
2 rue Ambroise Paré, 5010 Paris, France
e-mail: bruno-megarbane@wanadoo.fr
Tel.: +33-1-49959030
Fax: +33-1-49956578

S. W. Borron
Department of Emergency Medicine,
George Washington University School
of Medicine and International Toxicology
Consultants, LLC,
Washington, D.C., USA

Poisonings involving ethylene glycol (EG) and methanol are relatively uncommon, but remain important causes of suicide or epidemic poisonings, resulting in multiple deaths and serious sequelae [1]. Toxicity is related to the production of toxic metabolites by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (AldDH) (Fig. 1). The accumulation of glycolate (in EG poisoning) or formate (in methanol poisoning) results in an anion gap metabolic acidosis. In addition, methanol may induce irreversible visual impairment, while EG causes acute renal

Abstract *Background:* Ethylene glycol (EG) and methanol are responsible for accidental, suicidal, and epidemic poisonings, resulting in death or permanent sequelae. Toxicity is due to the metabolic products of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase. Conventional management of these intoxications consists of ethanol and hemodialysis. Fomepizole, a potent ADH inhibitor, has largely replaced antidotal ethanol use in France and two recent prospective U.S. trials definitively established its efficacy. Fomepizole appears safer than ethanol and while no comparative study of efficacy exists, fomepizole is recommended as the first-line antidote. *Focus:* Fomepizole, administered early in EG intoxication, prevents renal injury. In the absence of renal failure, EG clearance is rapid, avoiding the need for prolonged fomepizole administration. The long elimination half-life of methanol poisonings, with absent hemodialysis,

necessitates prolonged administration of fomepizole. In the U.S. trials, patients were dialyzed when plasma EG or methanol concentrations were ≥ 0.5 g/l. However, EG-poisoned patients treated with fomepizole prior to the onset of significant acidosis may not require hemodialysis. Indeed, fomepizole may also obviate the need for hemodialysis in selected methanol-poisoned patients, in the absence of neurological and ocular impairment or severe acidosis. When dialysis is indicated, 1 mg·kg⁻¹·h continuous infusion of fomepizole should be provided to compensate for its elimination. *Conclusions:* Fomepizole is an effective and safe first-line recommended antidote for EG and methanol intoxication. In selected patients, fomepizole may obviate the need for hemodialysis.

Keywords Methanol · Ethylene glycol · Acute poisoning · Fomepizole · Hemodialysis

failure [2, 3]. Either alcohol may cause death. Recommended management includes: 1) supportive care; 2) infusion of sodium bicarbonate to correct metabolic acidosis, to increase renal elimination of glycolate and formate, and to inhibit precipitation of calcium oxalate crystals; 3) antidotes, such as a competitive ADH substrate (ethanol) or inhibitor (fomepizole) to block ADH metabolism of the toxic alcohol; and 4) intermittent dialysis to remove the toxic alcohol and its toxic metabolites, to correct acidosis, and, in the case of methanol

Table 1 European dosage regimen of fomepizole in ethylene glycol poisoning: fomepizole is administered every 12 h, by oral or intravenous route, according to plasma ethylene glycol concentrations.

g/l	mmol/l	Loading dose	Fomepizole (mg/kg)				
			2nd dose T + 12 h	3rd dose T + 24 h	4th dose T + 36 h	5th dose T + 48 h	6th dose T + 60 h
6	96	15	10	10	10	7.5	5
3	48	15	10	10	10	7.5	
1.5	24	15	10	10	7.5		
0.75	12	15	10	7.5			
0.35	5.6	15	7.5				
0.1–0.3	1.6–5.5	15					

poisonings, to shorten the course of hospitalization [4, 5].

Fomepizole [4-methylpyrazole (4MP)] is a potent inhibitor of ADH with limited toxicity. It has been successfully used in France since 1981 in EG [6, 7] and methanol poisonings [8]. No lethality or significant morbidity has occurred with either alcohol when patients were treated before significant toxic metabolism occurred; all patients recovered from their poisonings. Two recent U.S. multi-center prospective clinical trials confirmed fomepizole's efficacy [9, 10]. Rapid resolution of acidosis accompanied clinical improvement, with no new symptoms of poisoning after the initiation of therapy. Renal injury did not occur if fomepizole was administered early in EG intoxication. Treatment with fomepizole resulted in alteration of the toxicokinetics of both EG and methanol, with a prolongation of their elimination and a reduction in glycolate and formate formation. The objectives of this review were to examine the remaining indications for supplementation of fomepizole therapy by hemodialysis in toxic alcohol poisonings.

Fomepizole is a safe and effective antidote

Fomepizole pharmacokinetics have been extensively studied. Although mostly administered by the intravenous route, fomepizole is rapidly and almost completely absorbed orally. Approximately one-third of our published cases of EG and methanol poisoning received this antidote orally [7, 8]. Fomepizole's volume of distribution has been reported to be in the range of 0.6–1.0 l/kg. Its plasma protein binding is low. Fomepizole has three metabolites: 4-hydroxymethylpyrazole, the only active metabolite—with approximately 1/3 the potency of the parent compound—4-carboxypyrazole, and a glucuronide metabolite [11]. Fomepizole is virtually entirely eliminated by saturable hepatic metabolism, with a K_m of 6 $\mu\text{mol/l}$, a concentration always markedly exceeded during therapeutic use [12]. Fomepizole's in vitro inhibitory constant for human ADH is 0.2 $\mu\text{mol/l}$. Its affinity for ADH is 500–1,000 times higher than that of ethanol. A plasma concentration of 10 $\mu\text{mol/l}$ inhibits formate accumulation in methanol-poisoned monkeys [11]. In the U.S. studies, complete inhibition was reached in each case

[9, 10], with plasma fomepizole concentrations exceeding the target concentration of 10 $\mu\text{mol/l}$. Elimination is characterized by dose-dependent, non-linear zero order kinetics, with a rate of 4–15 $\mu\text{mol}\cdot\text{l}^{-1}\cdot\text{h}$ [12, 13].

While fomepizole blocks ADH activity, repeated doses induce cytochrome P450, and particularly cytochrome P450 2E1, resulting in an increase in its own elimination rate after 48 h of treatment [12]. Thus, an increase to 15 mg/kg in patients treated over 48 h is currently recommended by practice guidelines developed by the American Academy of Clinical Toxicology, to account for its enhanced metabolism [14, 15]. However, it is noteworthy that fomepizole is expensive and a dosage regimen using the minimal effective cumulative dose remains to be determined. The French dosing regimen consists of a loading dose of 15 mg/kg followed by 10 mg/kg every 12 h until the alcohol concentration is <0.2 g/l. Borron et al. reported on a series of EG poisonings successfully treated with tapering doses of fomepizole [7]. Based on this clinical experience, a different dosage regimen is recommended in Europe (Table 1).

During hemodialysis, fomepizole is extracted with a mean extraction coefficient of 50±43%, a mean hemodialysis clearance of 99±33 ml/min, and a mean hourly extracorporeal extraction of 83±31% [16, 17]. Although not systematically validated, two different protocols were proposed to compensate for fomepizole loss in the dialysate. The U.S. manufacturer recommends a reduction in the dosing interval from 12 h to 4 h, while European authors have proposed a continuous IV infusion of 1–1.5 mg·kg⁻¹·h for the entire duration of the hemodialysis session following the initial loading dose [16, 17]. Since the duration of hemodialysis depends on the initial plasma EG or methanol concentration, the continuous infusion protocol appears better adapted than a shortening of the dosing interval. This regimen appears simpler and is sufficient to maintain fomepizole above the minimally effective concentrations (>10 $\mu\text{mol/l}$). However, the dosage of fomepizole during continuous veno-venous hemodiafiltration or continuous arteriovenous hemodialysis and the pharmacokinetics in patients with liver failure are not known. In patients with normal renal function, the renal clearances of EG and methanol are reported to be about 20 ml/min and 1 ml/min, respectively [14, 15].

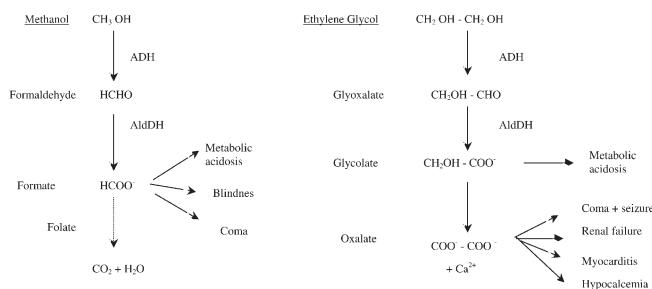


Fig. 1 Pathogenesis of methanol and ethylene glycol poisonings. The principal symptoms are related to the toxic metabolites resulting from degradation of the alcohol by alcohol (ADH) and aldehyde (AldDH) dehydrogenases.

Fomepizole administration results in first-order elimination of the toxic alcohols with a prolonged half-life, respectively 20 h and 54 h, for EG and methanol [9, 10, 18].

The contraindications of fomepizole administration are previously known allergy to pyrazole derivatives (such as phenylbutazone) and pregnancy. Case series and clinical trials indicate that fomepizole is well tolerated at therapeutic doses, although headache (12%), nausea (11%), dizziness (7%), and injection site irritation were reported [9, 10]. Other adverse reactions included rash, lymphangitis, vomiting, diarrhea, abdominal pain, tachycardia, hypotension, vertigo, slurred speech, inebriation, fever, mild transient eosinophilia, and slight increases in hepatic transaminases, none requiring discontinuation of therapy. In human volunteers, therapeutic doses of fomepizole (10–20 mg/kg) caused a 40% reduction in the rate of elimination of ethanol (0.5–0.7 g/kg). Conversely, ethanol was demonstrated to inhibit fomepizole metabolism, consequently increasing its blood concentration [13]. Thus, previous ethanol intake or administration before fomepizole therapy does not decrease the efficiency of the antidotal therapy. However, the clinical relevance of the effect of fomepizole on ethanol elimination remains to be determined. Although not formally studied in children,

several pediatric cases suggest clinical efficacy without severe side effects [19, 20], other than nystagmus [21].

Therapeutic concentrations are reliably achieved with the proposed dosing regimens and no severe central nervous system or liver toxicity or hypoglycemia occurs with fomepizole, in contrast with ethanol therapy. Ethanol therapy requires blood concentration monitoring and intravenous glucose administration in an intensive care unit (ICU), especially for pediatric poisonings [22]. Monitoring of therapeutic concentrations of fomepizole does not appear necessary. Therefore, considering its demonstrated efficacy and safety, we recommend fomepizole as a first-line antidote. In the case of suspicion of toxic alcohol ingestion or metabolic acidosis with elevated anion gap unexplained by an equivalent increase in serum lactate concentration, we suggest the administration of a loading dose of fomepizole while awaiting definitive diagnosis.

Hemodialysis and toxic alcohol poisoning

Hemodialysis is considered to be an integral part of the treatment of toxic alcohol poisonings to expedite removal of the alcohol and its metabolites, thus reducing the duration of antidotal treatment. Ethylene glycol and methanol are efficiently cleared by dialysis (Table 2). The traditional end-point of dialysis is a plasma concentration of the toxic alcohol <0.2 g/l, with resolution of acid-base disturbances and the osmolar gap [14, 15]. More recently, a simple method to estimate the required dialysis time was validated [23]. The required time (RDT) to reach a 5 mmol/l toxicant concentration is estimated as follows: RDT (h) = [-V.Ln(5/A)]/0.06 k, with V (l) representing the Watson estimation of total body water, A (mmol/l) the initial toxicant concentration, and k (ml/min) 80% of the manufacturer-specified dialyzer urea clearance. In this study, there was no difference between the predicted hemodialysis duration (7.6±1.9 h) and the actual duration employed using hourly concentration sampling (7.4±1.9 h).

Table 2 Toxicokinetic parameters of ethylene glycol and methanol and their modifications in relation to hemodialysis or antidotal treatment.

	Ethylene glycol	Methanol
Lethal dose	1.4–1.6 ml/kg	1.2 ml/kg (risk of blindness: 10–15 ml)
Molecular weight	62.4 g	32.04 g
Distribution volume	0.5–0.8 l/kg	0.6–0.77 l/kg
Elimination	Zero or 1st order	Zero order
Total body clearance	70 ml/min	11 ml/min
Renal clearance ^a	17–39 ml/min	1 ml/min
Half-life + fomepizole	~20 h	~54 h
+ ethanol	11–18 h	30–52 h
Half-life under dialysis	150–210 min	197–219 min
Dialysis clearance ^b	192–210 ml/min	95–176 ml/min
Main metabolite clearance ^c	254 ml/min	223 ml/min

^a Dependent on renal function

^b Dependent on blood flow during hemodialysis

^c Glycolate regarding ethylene glycol and formate regarding methanol

Table 3 Revised recommendations for hemodialysis in ethylene glycol and methanol poisoning [10, 11, 16, 17, 27].

Ethylene glycol poisoning:	
Arterial pH <7.10 ⁹ or 7.25–7.30 [16]	
Drop in arterial pH >0.05 resulting in a pH outside the normal range despite bicarbonate infusion	
Inability to maintain arterial pH >7.3 despite bicarbonate therapy	
Decrease in bicarbonate concentration >5 mmol/l, despite bicarbonate therapy	
Renal failure (serum creatinine concentration >265 µmol/l or rise in the serum creatinine by >90 µmol/l [10])	
Deteriorating vital signs despite intensive supportive care	
Initial plasma e.g., concentration ≥ 0.5 g/l (8.1 mmol/l) unless fomepizole is administered in the absence of both renal dysfunction and significant acidosis ^a	
Methanol poisoning:	
Initial arterial pH <7.10 ⁹ or 7.25–7.30 [16]	
Drop in arterial pH >0.05 resulting in a pH outside the normal range despite bicarbonate infusion	
Inability to maintain arterial pH >7.3 despite bicarbonate therapy	
Decrease in bicarbonate concentration >5 mmol/l, despite bicarbonate therapy	
Visual impairment	
Renal failure	
Deteriorating vital signs despite intensive supportive care	
Initial plasma methanol concentration ≥ 0.5 g/l (15.6 mmol/l) ^a	
Rate of methanol decline <0.1 g/l (3.1 mmol/l) per 24 h	

^a The recommendation for routine hemodialysis on the basis of serum concentrations alone has been recently called into question

Hemodialysis and ethylene glycol poisoning

Hemodialysis is typically recommended in case of severe or refractory metabolic acidosis, deteriorating vital signs, and at the onset of acute renal failure (Table 3). A serum EG concentration above 0.5 g/l (8.1 mmol/l) has been considered a symptom-independent indication, although this is debated [14]. In the U.S. study, 17 of 19 EG-poisoned patients treated with fomepizole were hemodialysed [9]. Among them, 18 survived, whereas only one died secondary to a myocardial infarction. All patients who developed renal injury had admission plasma glycolate concentrations >0.98 g/l (12.9 mmol/l). Renal elimination and hemodialysis are the only significant routes of EG elimination, as long as fomepizole concentrations are maintained well above 10 µmol/l [18]. Hemodialysis effectively clears glycolate, with an elimination half-life of 155±474 min, compared to the spontaneous elimination half-life of 625±474 min [24].

In a retrospective study, we demonstrated the lack of requirement for systematic dialysis in the management of EG poisoning treated with fomepizole [7]. We described 11 significantly EG-poisoned patients, among whom 21% presented with coma, 34% metabolic acidosis, and 11% an initial plasma creatinine >110 µmol/l. Hemodialysis was performed in only three of these 11 patients, two with renal insufficiency and acidosis and one with a very high EG concentration (8.27 g/l). Among the seven patients with normal renal function, no subsequent deterioration was noted. Only one patient died with severe multiorgan failure, the onset of which preceded fomepizole administration. Patients who were dialyzed were significantly more acidotic than those who were not. In summary, patients treated with fomepizole prior to the onset of

significant acidosis did not require hemodialysis. An EG concentration above 0.5 g/l (8.1 mmol/l) should no longer be considered as an independent criterion for hemodialysis in patients treated with fomepizole [25]. The recommended dialysis criteria are currently significant metabolic acidosis, renal failure, electrolyte imbalances unresponsive to conventional therapy, and deteriorating vital signs despite intensive supportive care [14].

Initial serum glycolic acid concentration appears to be a good indicator for hemodialysis; however, it is not readily available in most hospitals. Initial glycolic acid >10 mmol/l predicts acute renal failure, with a sensitivity of 100%, a specificity of 94% and an efficiency of 98% [26]. In a retrospective study of 41 EG-poisoned patients, dialysis was unnecessary, regardless of EG level, if glycolic acid was ≤8 mmol/l in patients receiving antidote. Anion gap >20 mmol/l or pH <7.30, but not EG concentration, were predictive of acute renal failure [26].

Hemodialysis and methanol poisoning

In methanol poisonings, due to its long elimination half-life, antidote administration clearly must be prolonged, whereas normal renal clearance of EG appears sufficient to avoid a prolonged course of fomepizole. The usual criteria for hemodialysis include severe acidosis, the presence of visual impairment or a plasma methanol concentration >0.5 g/l (15.6 mmol/l) (Table 3). In an U.S. study, seven of 11 methanol-poisoned patients treated with fomepizole were also hemodialysed [10]. Among these, nine survived, whereas two, with the most elevated formic acid concentrations, died from brain anoxia. Moreover, in other reported methanol poisonings treated

with fomepizole, hemodialysis was systematically employed [27, 28]. Low pH, bicarbonate, and elevated anion gap correlate independently with formate concentration [29]. However, although dialysis clears formate, surprisingly, it may not significantly enhance endogenous elimination (half-life: 150±37 min versus 205±90 min [29], although this is debated [30]. We treated an asymptomatic 35-year-old patient who refused dialysis for combined methanol (1.46 g/l) and isopropanol (0.39 g/l) poisoning [31]. Fomepizole (16 doses, cumulative dose: 96.6 g) appeared effective in blocking the toxic metabolism. In an outbreak of epidemic methanol poisoning in Cambodia, numerous patients were treated with intravenous fomepizole alone, as hemodialysis was not available. While follow-up was limited, no cases of recurrent or worsening toxicity were observed in this series [personal communication, Stephen W. Borron]. In poisonings involving high methanol concentrations, without severe acidosis or visual impairment, patients have been successfully treated by prolonged repeated doses of fomepizole without dialysis. We treated four patients with methanol levels >0.5 g/l with only fomepizole without hemodialysis [8]. They recovered without sequelae. However, in this retrospective analysis of 14 methanol-exposed patients, metabolic acidosis was significantly more severe among patients undergoing hemodialysis, suggesting that they were more severely intoxicated.

Visual impairment is traditionally considered an absolute indication for dialysis. Two case reports suggest that this recommendation is reasonable. A 42-year-old man, with central blindness completely recovered after combined fomepizole and hemodialysis [32]. A 60-year-old man, with blurred vision and alteration in his evoked potentials examinations, experienced a complete reversal of his visual impairment within 20 h after combined fomepizole and hemodialysis [33]. Moreover, fomepizole appeared safe in patients exhibiting retinal toxicity, despite its potential to inhibit retinol dehydrogenase (ADH isoenzyme, essential to vision) [32]. Recent recommendations limit dialysis indications to severe acidosis, visual signs or symptoms, deteriorating vital signs despite intensive care, renal failure, significant electrolyte disturbance unresponsive to conventional therapy, or serum methanol concentration ≥ 0.5 g/l [15]. Additional clinical experience with prolonged fomepizole administration may obviate the need to dialyze patients on the basis of elevated serum methanol concentration alone. After initial hemodialysis, ocular abnormalities may persist and should thus be considered as an indication for continued dialysis.

Critical analysis of the role of hemodialysis

Although ethanol and hemodialysis for many years constituted the recommended therapy, it is unlikely that ap-

plying principles of evidence-based medicine would justify such recommendations now, given the significant experience with fomepizole and dialysis [25]. While a comparison of fomepizole with ethanol (+/- hemodialysis) would be of interest, such a study has not and likely will not be done for a variety of reasons. Nonetheless, until it is demonstrated that ethanol therapy results in equivalent outcomes, it is difficult not to recommend fomepizole. There are frequent references to the minimal cost of parenteral ethanol in comparison with the relatively high cost of fomepizole. Such comparisons ignore the critical issue of laboratory costs for monitoring serum ethanol and blood glucose, the increased nursing care required for inebriated patients, and the requirement for intensive care (which may not be necessary in patients receiving fomepizole, in the absence of extant toxicity). Considering the high cost of fomepizole (about \$1,000 per gram), smaller hospital centers that only occasionally see EG or methanol poisoning, might prefer continuing to stock inexpensive and readily available parenteral ethanol. However, it should be kept in mind that the suggested shelf life of fomepizole is 3 years and that, in some cases, the manufacturer will replace it at no charge after this period, rendering it economical even for smaller emergency departments to have this antidote in their armamentarium.

Why is it worthwhile to confirm that fomepizole may obviate hemodialysis under certain conditions? First, there is a significant downside to the use of hemodialysis: it is not universally available, rendering it difficult in case of epidemic poisonings. It represents an invasive technique with risks of adverse effects. Moreover, some data suggest that it does not modify formate kinetics (elimination half-life). Furthermore, hemodialysis of poisoned patients often requires hospitalization in an ICU. If sig-

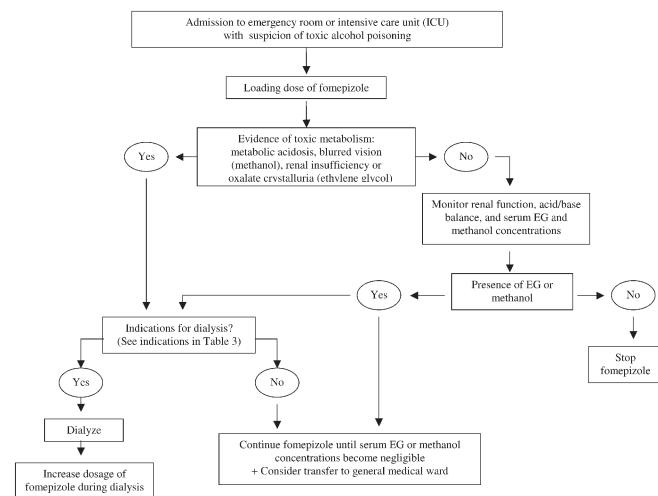


Fig. 2 Proposed algorithm for treatment of EG and methanol-poisoned patients. This algorithm is based on series and case reports.

nificant toxicity and hemodialysis can be avoided by the early administration of fomepizole, ICU admissions may be limited to a relatively brief (24 h) period of observation (Fig. 2).

There are also advantages to the use of fomepizole in comparison with ethanol: fomepizole is a more potent ADH inhibitor with a wider therapeutic index, a longer duration of action, easier dosing, and more predictable kinetics. There is no need for blood concentration monitoring. Treatment is well tolerated, even during prolonged administration (up to 8 days), whereas there are no similar data concerning ethanol. Pancreatitis, seen after certain cases of methanol poisoning, has been attributed to prolonged 'therapeutic' administration of ethanol [34]. Thus, ethanol, in our estimation, should be administered only when fomepizole is unavailable or contraindicated. Given its safety, especially in patients who may subsequently be found not to be poisoned with toxic alcohols, fomepizole permits a margin of diagnostic error. In selected exposed patients, fomepizole may obviate the need for hemodialysis. However, the risks, costs, and inconvenience of prolonged hospitalization and the cost of fomepizole must be weighed against those of hemodialysis. Keeping patients with high serum methanol concentrations monitored in an ICU for a long period is considered by some authors as untenable [15]. Whether these patients, in the absence of initial toxicity, actually require prolonged intensive care monitoring has yet to be determined, however.

Other experiences with fomepizole in alcohol and glycol poisonings

Fomepizole has been used to treat other toxic alcohol poisonings, including diethylene and triethylene glycols [35], methanol and isopropanol [31], butoxyethanol [36], and 1,4 butanediol [37] poisonings. In one case of diethylene glycol poisoning, a patient was treated with combined fomepizole and hemodialysis [38]. Fomepizole inhibits the accumulation of acetaldehyde in disulfiram reactions [39], attenuating facial flushing, tachycardia, and vasodilatation. These cases serve solely as examples of potential indications for fomepizole. We must underscore that before fomepizole or any other antidote is employed in the case of a toxic alcohol exposure, the metabolism of that alcohol should be understood and the antidote's safety and efficacy for that particular treatment demonstrated. Such an understanding will avoid unintended blockade of detoxifying metabolism or induction of activating metabolism.

Conclusion

Fomepizole appears safe and effective in preventing or diminishing EG and methanol toxicity. While antidotal therapy without hemodialysis appears to be efficacious in a number of cases of uncomplicated poisonings, further experience is needed to clearly define the indications for associated hemodialysis.

References

- Watson WA, Litovitz TL, Rodgers GC Jr, Klein-Schwartz W, Youniss J, Rose SR, Borys D, May ME (2003) 2002 annual report of the American Association of poison control centers toxic exposure surveillance system. *Am J Emerg Med* 21:353–421
- Hylander B, Kjellstrand CM (1996) Prognostic factors and treatment of severe ethylene glycol intoxication. *Intensive Care Med* 22:546–552
- Liu JJ, Daya MR, Carrasquillo O, Kales SN (1998) Prognostic factors in patients with methanol poisoning. *J Toxicol Clin Toxicol* 36:175–181
- Jacobsen D, McMullan KE (1997) Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol* 35:127–143
- Mégarbane B, Baud F (2003) Is there a remaining place for hemodialysis in toxic alcohol poisonings treated with fomepizole? *J Toxicol Clin Toxicol* 41:396–397 [abstr]
- Baud FJ, Galliot M, Astier A, Bien DV, Garnier R, Likforman J, Bismuth C (1988) Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. *N Engl J Med* 319:97–100
- Borron SW, Mégarbane B, Baud FJ (1999) Fomepizole in treatment of uncomplicated ethylene glycol poisoning. *Lancet* 354:831
- Mégarbane B, Borron SW, Trout H, Hantson P, Jaeger A, Krencker E, Bismuth C, Baud FJ (2001) Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med* 27:1370–1378
- Brent J, McMullan K, Phillips S, Burkhardt KK, Donovan JW, Wells M, Kulig K (1999) Fomepizole for the treatment of ethylene glycol poisoning. *Methylpyrazole for Toxic Alcohols Study Group*. *N Engl J Med* 340:832–838
- Brent J, McMullan K, Philipps S, Aaron C, Kulig K, Methylpyrazole for Toxic Alcohols Study Group (2001) Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 344:424–429
- McMullan KE, Hedström KG, Tolf BR, Ostling-Wintzell H, Blomstrand R (1980) Studies on the metabolic interactions between 4-methylpyrazole and methanol using the monkey as an animal model. *Arch Biochem Biophys* 199:606–614
- Jacobsen D, Barron SK, Sebastian CS, Blomstrand R, McMullan KE (1989) Non-linear kinetics of 4-methylpyrazole in healthy human subjects. *Eur J Clin Pharmacol* 37:599–604
- Jacobsen D, Sebastian CS, Dies DF, Breau RL, Spann EG, Barron SK, McMullan KE (1996) Kinetic interactions between 4-methylpyrazole and ethanol in healthy humans. *Alcohol Clin Exp Res* 20:804–809

14. Barceloux DG, Krenzelok EO, Olson K, Watson W (1999) American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *J Toxicol Clin Toxicol* 37:537–560
15. Barceloux DG, Bong GR, Krenzelok EP, Cooper H, Vale JA, American Academy of Clinical Toxicology ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning (2002) American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 40:415–446
16. Faissel H, Houze P, Baud FJ, Schermann JM (1995) 4-methylpyrazole monitoring during hemodialysis of ethylene glycol intoxicated patients. *Eur J Clin Pharmacol* 49:211–213
17. Jobard E, Harry P, Turcant A, Roy PM, Allain P (1996) 4-methylpyrazole and hemodialysis in ethylene glycol poisoning. *J Toxicol Clin Toxicol* 34:379–381
18. Sivilotti MLA, Burns MJ, McMullan KE, Brent J (2001) Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. *Ann Emerg Med* 36:114–125
19. Martin Caravati E, Heileson HL, Jones M (2004) Treatment of severe pediatric ethylene glycol intoxication without hemodialysis. *J Toxicol Clin Toxicol* 42:255–259
20. Brown MJ, Shannon MW, Woolf A, Boyer EW (2001) Childhood methanol ingestion treated with fomepizole and hemodialysis. *Pediatrics* 108:77–79
21. Benitez JG, Swanson-Bearman B, Krenzelok EP (2000) Nystagmus secondary to fomepizole administration in a pediatric patient. *J Toxicol Clin Toxicol* 38:795–798
22. Roy M, Bailey B, Chalut D, Senécal PE, Gaudreault P (2003) What are the adverse effects of ethanol used as an antidote in the treatment of suspected methanol poisoning in children. *J Toxicol Clin Toxicol* 41:155–161
23. Hirsch DJ, Jindal KK, Wong P, Fraser AD (2001) A simple method to estimate the required dialysis time for cases of alcohol poisoning. *Kidney Int* 60:2021–2024
24. Moreau CL, Kerns W II, Tomaszewski CA, McMullan KE, Rose SR, Ford MD, Brent J (1998) Glycolate kinetics and hemodialysis in ethylene glycol poisoning. *J Toxicol Clin Toxicol* 36:659–666
25. Watson WA (2000) Ethylene glycol toxicity: closing in on rational, evidence-based treatment. *Ann Emerg Med* 36:139–141
26. Porter WH, Rutter PW, Bush BA, Papas AA, Dunnington JE (2001) Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis. *J Toxicol Clin Toxicol* 39:607–615
27. Hantson P, Wallemacq P, Brau M, Vanbinst R, Haufroid V, Mahieu P (1999) Two cases of acute methanol poisoning partially treated by oral 4-methylpyrazole. *Intensive Care Med* 25:528–531
28. Burns MJ, Graudins A, Aaron CK, McMullan K, Brent J (1997) Treatment of methanol poisoning with intravenous 4-methylpyrazole. *Ann Emerg Med* 30:829–832
29. Kerns W 2nd, Tomaszewski C, McMullan K, Ford M, Brent J, META Study Group (2003) Methylpyrazole for toxic alcohols: formate kinetics in methanol poisoning. *J Toxicol Clin Toxicol* 41:257–258
30. Yip L, Jacobsen D (2002) Endogenous formate elimination and total body clearance during hemodialysis. *J Toxicol Clin Toxicol* 40:137–143
31. Bekka R, Borron SW, Astier A, Sandouk P, Bismuth C, Baud FJ (2001) Treatment of methanol and isopropanol poisoning with intravenous fomepizole. *J Toxicol Clin Toxicol* 39:59–67
32. Sivilotti ML, Burns MJ, Aaron CK, McMullan KE, Brent J (2001) Reversal of severe methanol-induced visual impairment: no evidence of retinal toxicity due to fomepizole. *J Toxicol Clin Toxicol* 39:627–631
33. Essama Mbia JJ, Guerit JM, Haufroid V, Hantson P (2002) Fomepizole therapy for reversal of visual impairment after methanol poisoning: a case documented by visual evoked potentials investigation. *Am J Ophthalmol* 134:914–916
34. Hantson P, Mahieu P (2000) Pancreatic injury following acute methanol poisoning. *J Toxicol Clin Toxicol* 38:297–303
35. Borron SW, Baud FJ, Garnier R (1997) Intravenous 4-methylpyrazole as an antidote for diethylene glycol and triethylene glycol poisoning: a case report. *Vet Hum Tox* 39:26–28
36. Osterhoudt KC (2002) Fomepizole therapy for pediatric butoxyethanol intoxication. *J Toxicol Clin Toxicol* 40:929–930
37. Mégarbane B, Fompeydie D, Garnier R, Baud FJ (2002) Treatment of a 1,4-butanediol poisoning with fomepizole. *J Toxicol Clin Toxicol* 40:77–80
38. Brophy PD, Tenenbein M, Gardner J, Bunchman TE, Smoyer WE (2000) Childhood diethylene glycol poisoning treated with alcohol dehydrogenase inhibitor fomepizole and hemodialysis. *Am J Kidney Dis* 35:958–962
39. Lindros KO, Stowell A, Pikkarainen P, Salaspuro M (1981) The disulfiram (antabuse) – alcohol reaction in male alcoholics: its efficient management by 4-methylpyrazole. *Alcohol Clin Exp Res* 5:528–530