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REVIEW

Ethylene glycol or methanol intoxication: which antidote should be used, fomepizole or ethanol?

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ABSTRACT

Ethylene glycol (EG) and methanol poisoning can cause life-threatening complications. Toxicity of EG and methanol is related to the production of toxic metabolites by the enzyme alcohol dehydrogenase (ADH), which can lead to metabolic acidosis, renal failure (in EG poisoning), blindness (in methanol poisoning) and death. Therapy consists of general supportive care (e.g. intravenous fluids, correction of electrolytes and acidaemia), the use of antidotes and haemodialysis. Haemodialysis is considered a key element in the treatment of severe EG and methanol intoxication and is aimed at removing both the parent compound and its toxic metabolites, reducing the duration of antidotal treatment and shortening the hospital observation period. Currently, there are two antidotes used to block ADH-mediated metabolism of EG and methanol: ethanol and fomepizole. In this review, the advantages and disadvantages of both antidotes in terms of efficacy, safety and costs are discussed in order to help the physician to decide which antidote is appropriate in a specific clinical setting.

KEYWORDS

Haemodialysis, 4-methylpyrazole, poisoning, toxicity

INTRODUCTION

Ethylene glycol (EG) and methanol poisoning are associated with significant morbidity and mortality if left untreated. Poisoning may occur through attempted inebriation, unintentional ingestion, or intentional self-harm. EG is a common component of antifreeze and de-icing solutions. The majority of the information requests to the Dutch Poisons Information Centre (DPIC) regarding EG involve exposure to EG-containing antifreeze or de-icing solutions (~900 exposures reported from 2005 until 2012).

Methanol is present as a solvent in many household products, such as antifreeze, cleaning solutions, dyes, and paint removers. The consumption of illegally produced or homemade alcoholic beverages containing relatively high levels of methanol entails another risk. Several large outbreaks of methanol poisoning have occurred in the past decades, which have resulted in numerous deaths.[1] For example, in a large methanol outbreak in Norway, 17 patients died after consumption of illegally produced liquor containing ~20% methanol.[2] From 2005 until 2012, the DPIC was consulted about ~800 methanol exposures, mainly by ingestion of methylated spirits (containing ~3% methanol), formaldehyde solutions (~15% methanol) or pure methanol.

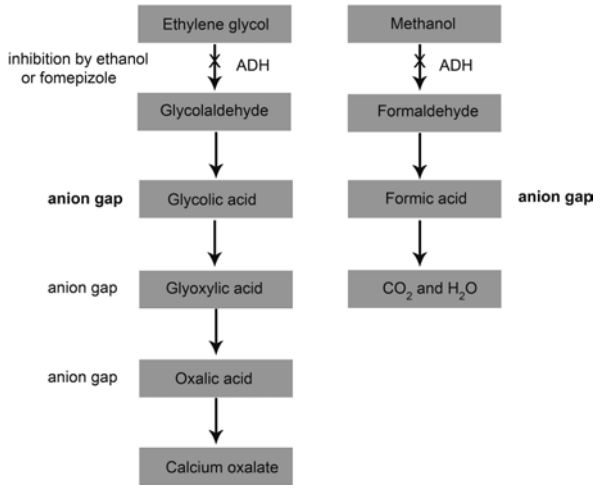
CLINICAL FINDINGS IN ETHYLENE GLYCOL POISONING

Acute EG intoxication can proceed through three distinct stages: central nervous system (CNS) depression, followed by cardiopulmonary dysfunction, and finally renal dysfunction (0.5-12 hours, 12-24 hours and 24-72 hours, respectively, after ingestion). However, the onset and progression of the clinical course is often not consistent or predictable.[3]

Toxicity of EG is related to the production of toxic metabolites by the hepatic enzyme alcohol dehydrogenase (ADH). EG is oxidised to glycolaldehyde by ADH, and subsequently converted to glycolic acid, glyoxylic acid and oxalic acid (*figure 1*). Oxalic acid binds to calcium, leading to the formation of insoluble calcium oxalate crystals, sometimes leading to hypocalcaemia. These calcium oxalate crystals deposit in several organs,[4-6] causing acute renal failure and myocardial, neurological and pulmonary dysfunction.[7]

Initially, only mild confusion or stupor is present, and patients may experience nausea and vomiting. As the intoxication progresses, neurological symptoms can become more profound. EG may cause severe neurological deficits, and even mimic a clinical state of brain death.[8] Metabolic acidosis arises from accumulation of glycolic acid and oxalic acid. To compensate for metabolic acidosis, patients develop hyperventilation (Kussmaul breathing). Hypocalcaemia can lead to hyperreflexia and cardiovascular complications.[3,7,9] After 24-72 hours, acute renal failure may become manifest. In severe intoxication, renal failure appears early and progresses to anuria. In severe cases, multiorgan failure and death occur.[10] Some analysers falsely measure increased levels of lactic acid when glycolic acid is present, because glycolic acid has almost the same chemical structure as lactic acid. This can lead to misdiagnosis and a delay in the treatment of EG poisoning.[11]

Figure 1. *Metabolism of EG and methanol. The antidotes ethanol and fomepizole inhibit ADH-mediated metabolism of EG and methanol to toxic metabolites. The toxic metabolites contributing to the anion gap are indicated by a bold (highly contributing) and a regular letter (modestly contributing).*[7]



ADH = alcohol dehydrogenase

Although the lethal dose of EG in humans has been reported to be ~1.5 ml/kg bodyweight, death has been associated with lower amounts, and survival has been reported with much greater amounts.[7] This could indicate individual susceptibility to the adverse effects of EG.

CLINICAL FINDINGS IN METHANOL POISONING

Toxicity of methanol is also related to the production of toxic metabolites by ADH. Methanol is oxidised to formaldehyde by ADH, which can be subsequently oxidised to formic acid, which is the major toxic metabolite of methanol (*figure 1*).

Depending on the co-ingestion of ethanol, onset of symptoms ranges from 40 minutes to 72 hours with an average of 24 hours.[3] Early stages of methanol poisoning are mild and transient, manifesting as mild euphoria or inebriation, followed by a latent phase lasting from 6 to 30 hours during which toxic methanol metabolites are formed.[3] The toxic metabolite formic acid is primarily responsible for the retinal and optic nerve damage, probably caused by disruption of mitochondrial electron transport.[12] This damage results in visual disturbances, which are reversible in most patients. However, permanent visual sequelae have been described following severe intoxication.[10,13,1] CNS manifestations include headache, lethargy and confusion in mild-to-moderate intoxication and Parkinson-like extrapyramidal symptoms in severe intoxication. Poor prognostic signs include severe metabolic acidosis, cardiovascular shock, seizures or coma. Respiratory failure or sudden respiratory arrest is the most common cause of death in methanol poisoning.[3] The lethal dose of pure methanol is generally estimated to be 1-2 ml/kg bodyweight. However, permanent blindness and deaths have been reported with 0.1 ml/kg bodyweight.[3]

LABORATORY FINDINGS IN ETHYLENE GLYCOL AND METHANOL POISONING

In many hospital laboratories, no direct measurement of EG or methanol concentrations, or their toxic metabolites, is available on a 24-hour basis. The measurement of osmolal (OG) and anion gap (AG) can be useful in the diagnosis of EG and methanol intoxication. Early in the intoxication, serum osmolality can be increased, which is caused by increased EG or methanol concentrations. As methanol and EG metabolism proceeds, the OG decreases and, because of accumulation of toxic metabolites, the AG increases (*figure 1*). Later on, the osmolality might not be increased anymore, while AG is still increased by the toxic metabolites. In EG intoxication, AG can also

be increased by EG-induced kidney failure.[7,15] In EG poisoning, envelop-shaped and needle-shaped oxalate crystals may be present in urine.[7,16]

TREATMENT OF ETHYLENE GLYCOL AND METHANOL POISONING

In case of EG or methanol exposure, immediate consultation with a poison control centre is strongly recommended. Patients with moderate-to-severe EG or methanol poisoning should be admitted to a medical ward, and in case of life-threatening symptoms, to an intensive care unit. Because EG and methanol are rapidly absorbed, gastrointestinal decontamination using gastric lavage or activated charcoal is not recommended.[9] However, the induction of vomiting directly after ingestion of massive amounts of EG or methanol may be useful.

General supportive care, i.e. mechanical ventilation, intravenous fluids, and vasopressors, may be indicated in severe intoxication.[9,10] To correct severe acidaemia (pH <7.3), the administration of sodium bicarbonate is recommended.[9,10] Calcium suppletion is indicated in EG intoxication if hypocalcaemia, due to formation of calcium oxalate crystals, significantly contributes to symptoms such as muscle spasms or seizures.[9]

Currently, there are two antidotes used to block ADH-mediated metabolism of EG and methanol in order to reduce formation of toxic metabolites: ethanol, a competitive ADH substrate, and fomepizole (4-methylpyrazole), an ADH inhibitor (*figure 1*). Today, in North-American and Western-European countries, fomepizole is considered by some authors to be the first-line antidote for EG and methanol poisoning.[9,10] Fomepizole was approved in the United States for the treatment of EG and methanol poisoning in 1997 and 2000, respectively. Fomepizole and ethanol are most effective when given in the early phase of the intoxication, before significant levels of the toxic metabolites are formed. Criteria for the initiation of antidote administration in EG and methanol poisoning are shown in *table 1*.[17,18] Antidotal treatment considerably increases the half-life of EG and methanol (*table 2*). Haemodialysis is considered an integral part of the treatment of severe EG and methanol poisoning and is aimed at removing both the parent compound and its toxic metabolites, to correct metabolic acidosis and electrolyte disturbances, thereby reducing the duration of antidotal treatment and, in most cases, the duration of hospitalisation.[9]

Current criteria for haemodialysis in EG and methanol poisoning, which are based more on clinical experience rather than on research data, include an initial plasma methanol or EG concentration ≥500 mg/l (8.1 mmol EG/l or 15.6 mmol methanol/l). Other criteria are severe metabolic acidosis, renal failure, electrolyte imbalances unresponsive to conventional therapy, deterioration of vital signs despite intensive supportive care or visual disturbances (in methanol poisoning).[9,10,17,18] However, haemodialysis carries a low risk of bleeding, air embolism, thrombosis, hypovolaemia, hypotension, electrolyte abnormalities and infections.

Several adjunctive therapies with limited demonstration of efficacy have been suggested. In EG poisoning, pyridoxine and thiamine could prevent the formation of oxalic acid by facilitating the conversion of glyoxylic acid to non-toxic metabolites.[16,19] In methanol poisoning, the administration of folic acid might theoretically be beneficial, as formic acid is converted to carbon dioxide and water by tertrahydrofolate synthetase, an enzyme that is dependent on folic acid.[10,19]

Table 1. *Criteria for initiating antidotal therapy in ethylene glycol (EG) and methanol intoxication*[9,10,17,18]

Criteria
1. Documented plasma concentration ≥200 mg/l (3.2 mmol/l for EG and 6.2 mmol/l for methanol) OR 2. Documented recent history of ingesting toxic amounts of EG/methanol and osmolal gap >10 mOsm/l OR 3. Suspected EG/methanol ingestion and at least 3 (for EG poisoning) or 2 (for methanol poisoning) of the following criteria: - Arterial pH <7.3 - Serum bicarbonate <20 mmol/l - Osmolal gap >10 mOsm/l - Oxalate crystalluria *(consider this criteria only for EG exposures)*

Table 2. *Half-lives of ethylene glycol (EG) and methanol and their alteration in relation to antidotal therapy and haemodialysis*

Treatment	Half-life EG	Half-life methanol
During poisoning (no treatment)	~3-9 h[17]	~8-28 h (at very low concentration: ~3 h)[44]
Fomepizole treatment	~14-20 h[42,43]	~50 h[46]
Ethanol treatment	~17 h[44]	~30-52 h[47]
Antidotal therapy combined with haemodialysis	~2.5-3.5 h[45]	~3.5 h[47]

ETHANOL VS FOMEPIZOLE

There are a number of reasons to prefer fomepizole as an antidote instead of ethanol[9,10,20] (*table 3*). Fomepizole has a higher potency to inhibit ADH, with a longer duration of action. The administration regimen is easy, including a fixed loading dose followed by intermittent bolus doses

Table 3. *Comparison of fomepizole and ethanol in the treatment of ethylene glycol (EG) and methanol poisoning*

	Fomepizole	Ethanol
Advantages	Higher affinity for ADH than ethanol	Inexpensive
	Minimal adverse effects	Available in most clinical centres
	Monitoring of fomepizole blood levels not necessary (standardised administration regime)	Traditionally used antidote: more clinical experience
	Hospitalisation in ICU in general not necessary	
	May obviate the need for haemodialysis in specific cases, although the hospital observation period needs to be extended, because of the increased half-life of methanol and EG	
Disadvantages	Expensive	Lower affinity for ADH than fomepizole
	Not available in all medical centres	Significant adverse effects possible: CNS depression, hypoglycaemia and hepatotoxicity. In case of depression of ventilation, intubation and artificial ventilation may be needed
	Limited shelf life (~3 years)	Adverse effects can confuse the interpretation of clinical course or response to therapy
	Less physician experience (compared with ethanol therapy)	Hospitalisation in ICU necessary during treatment
	Fomepizole increases half-life of methanol and EG, therefore also consider using haemodialysis	Requires intensive monitoring of ethanol and glucose blood levels
		When treatment is monitored by the osmolal gap (when EG or methanol measurements are unavailable), then it is important to realise that ethanol contributes to the osmolal gap
		Ethanol increases half-life of methanol and EG, therefore also consider using haemodialysis

ADH = alcohol dehydrogenase; CNS = central nervous system; ICU = intensive care unit.

every 12 hours, and there is no need for fomepizole blood concentration monitoring (*table 4*).

The fomepizole dose should be increased after 48 hours to account for an enhanced fomepizole clearance due to fomepizole-induced cytochrome P450 (CYP2E1) induction.[21] Haemodialysis efficiently removes fomepizole. Two different protocols are proposed to compensate for fomepizole loss in the dialysate (*table 4*).[9,10]

Fomepizole is generally well tolerated, although sometimes injection site irritation, nausea, dizziness, tachycardia, headache, eosinophilia, slight increases in hepatic transaminase, agitation and seizures were reported.[9,10,22-25] However, it is unknown whether most of these effects were due to the fomepizole treatment itself or to the EG or methanol poisoning.[10]

During ethanol therapy, regular ethanol blood concentration monitoring is necessary (every 1-2 hours), requiring frequent ethanol infusion adjustments. First, a loading dose of 600-1000 mg/kg should be administered, followed by a maintenance dose to maintain the target ethanol level (~1000-1500 mg/l).[26] This ethanol level leads to sufficient saturation of ADH, thereby inhibiting further metabolism of EG and methanol to their toxic metabolites. Individual variability, e.g. chronic alcohol abuse, influences the rate of ethanol metabolism. Therefore, the maintenance dose of ethanol should be increased in chronic alcohol abusers (*table 5*).[26] Like fomepizole, ethanol is also removed during haemodialysis. Therefore, the ethanol dose must be increased in patients undergoing haemodialysis, representing an additional difficulty. During ethanol therapy, significant mental status changes, hypoglycaemia (especially in paediatric and malnourished patients), liver toxicity or pancreatitis can occur. Ethanol therapy may therefore confuse the interpretation of the already complex clinical course of EG and methanol poisoning. Despite these disadvantages, ethanol is used as a first-line antidote for EG and methanol intoxication in some medical centres, especially due to its low costs, physician experience and the fact that it is readily available.[27]

In the Netherlands, the cost of fomepizole is ~150 € per 100 mg. In two prospective clinical trials,[10,22,23] EG- and methanol-intoxicated patients received a median of 3.5-4 doses of fomepizole (total fomepizole costs ~4500 € per treated patient weighing 70 kg). Ethanol itself is inexpensive. However, ethanol therapy requires ICU or high-care admission and regular determination of serum ethanol and blood glucose levels, which increases total treatment costs. *Table 3* summarises the advantages and disadvantages of fomepizole and ethanol in the treatment of EG and methanol intoxication.

Table 4. *Recommended doses of fomepizole for ethylene glycol (EG) and methanol poisoning*[9,10]

Fomepizole dosing scheme

For patients not undergoing haemodialysis
Loading dose (t=0 h): 15 mg/kg, followed by 10 mg/kg at t=12 h, t=24 h and t=36 h
After 48 h, fomepizole dose should be increased to 15 mg/kg every 12 h*

For patients undergoing haemodialysis: two proposed protocols
1. A reduction in time interval between fomepizole doses. Same doses administered to patients who are not undergoing haemodialysis, except that fomepizole is given 6 h after the first dose and every 4 h thereafter*
2. A continuous IV infusion of 1-1.5 mg/kg/h following the initial loading dose

***All doses are administered intravenously over a 30-minute period.**

Several authors suggest that the introduction of fomepizole has obviated the need for haemodialysis in specific patient groups, i.e. in patients without signs of renal or optical injury and with normal acid-base status.[10,28,29] Given the effectiveness in removing both the alcohols and the toxic metabolites, and the difficulty of rapid determination of EG and methanol levels, haemodialysis (in concert with fomepizole or ethanol) should always be considered in suspected cases and in patients with, for example, severe metabolic acidosis, electrolyte disturbances, renal failure or visual disturbances, or deterioration of vital signs despite intensive supportive care. Fomepizole and ethanol treatment increases the half-life of EG and methanol and therefore prolongs the necessity of clinical observation. Haemodialysis considerably reduces the half-life of these compounds and consequently will reduce hospital stay (*table 2*). Controlled, prospective studies would be useful in developing evidence-based guidelines, and aid in the decision to initiate haemodialysis in addition to antidotal therapy.

There has been no direct head-to-head comparison of ethanol and fomepizole in terms of efficacy, safety, or cost-effectiveness to provide evidence that fomepizole is superior to ethanol.[20] Interestingly, by using a physiologically based pharmacokinetic (PBPK) model, it was demonstrated that fomepizole, if administered early during an EG intoxication, can be more effective than ethanol in preventing the metabolism of EG to toxic metabolites.[30]

Beatty *et al.* performed a systematic review to investigate the efficacy and safety of ethanol and fomepizole as an antidote in EG and methanol poisoning in adults.[20] Mortality in patients treated with ethanol was ~22% for methanol and ~18% for EG. In patients administered fomepizole, mortality was lower: ~17% for methanol and ~4% for EG. However, because of the quality of the reported data it cannot be concluded that the mortality difference is due to the use of a specific antidote. In addition, the majority of case reports reported in this review from before the mid-1990s describe the use of ethanol, whereas fomepizole is much more commonly reported in recent years, when advances in general supportive care and haemodialysis have significantly improved patient outcomes. Lepik *et al.* investigated adverse drug events associated with ethanol and fomepizole in methanol or EG poisonings. Although

Table 5. *Recommended doses of ethanol for ethylene glycol (EG) and methanol poisoning*[26]

Ethanol dosing scheme *

Loading dose
0.6-1.0 g/kg intravenously (7.5-12.5 ml ethanol 10% solution in glucose/kg)
or
2.5 ml/kg orally 40% ethanol solution [44]

Maintenance dose (intravenously)
The maintenance dose can be calculated as follows:
Dose $_{maintenance}$ (g/h) = (target ethanol concentration x V_{max} x bodyweight in kg) / (K_m + target ethanol concentration)
V_{max} (maximum reaction rate): in children: 0.075 g/kg/h; in adults: 0.125 g/kg/h (occasional alcohol intake) and 0.175 g/kg/h (alcohol abusers)
K_m (Michaelis Menten constant): 0.138 g/l
Target ethanol concentration = 1000-1500 mg/l(1-1.5‰). Use for this calculation a target ethanol concentration of 1‰

Children: 0.8 ml ethanol 10% solution in glucose/kg/h
Adult (occasional alcohol intake): 1.4 ml ethanol 10% solution in glucose/kg/h
Alcohol abuser: 2.0 ml ethanol 10% solution in glucose/kg/h

Maintenance dose (intravenously) during haemodialysis
During haemodialysis, an additional dose of 1.9 ml ethanol 10% solution in glucose/kg/h should be administered intravenously (in addition to the calculated maintenance dose)

Children: 2.7 ml ethanol 10% solution in glucose/kg/h
Adult (occasional alcohol intake): 3.3 ml ethanol 10% solution in glucose/kg/h
Alcohol abuser: 3.9 ml ethanol 10% solution in glucose/kg/h

*** The target ethanol concentration is 1000-1500 mg/l (1-1.5‰)**[26]

there were several observational study limitations, results suggest a lower occurrence of adverse drug events with fomepizole compared with ethanol.[31]

USE OF FOMEPIZOLE IN CHILDREN

Few data are available on the use of fomepizole in the treatment of EG and methanol poisoning in paediatric patients.[32-40] Most of these case reports were evaluated by Brent *et al.*[41] These data suggest that fomepizole is safe and effective in the paediatric population using the same dosage regimen as that used for adults (*table 4*).[41] All patients recovered without sequelae. The only adverse reaction reported during fomepizole therapy in these children was transient nystagmus in a 6-year-old.[33] However, it is unclear whether this effect was related to fomepizole.

CONCLUSION

There is no conclusive scientific evidence whether ethanol or fomepizole should be used as first-line treatment of EG and methanol intoxication, as there has been no direct comparison between the two antidotes in terms of efficacy, safety, or cost-effectiveness. The decision to use fomepizole or ethanol is dependent on the availability and costs of the antidote, haemodialysis facilities, patient characteristics and physician experience with the specific antidote. If the treating physician has no experience with either antidote, then the treatment with fomepizole is easier, especially in the paediatric population.

REFERENCES

1. Lachenmeier DW, Rehm J, Gmel G. Surrogate alcohol: what do we know and where do we go? Alcohol Clin Exp Res. 2007;31:1613-24.
2. Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. J Intern Med. 2005;258:181-90.
3. Jammalamadaka D, Raissi S. Ethylene glycol, methanol and isopropyl alcohol intoxication. Am J Med Sci. 2010;339:276-81.
4. Froberg K, Dorion RP, McMartin KE. The role of calcium oxalate crystal deposition in cerebral vessels during ethylene glycol poisoning. Clin Toxicol (Phila). 2006;44:315-8.
5. McMartin K. Are calcium oxalate crystals involved in the mechanism of acute renal failure in ethylene glycol poisoning? Clin Toxicol (Phila). 2009;47:859-69.
6. Pomara C, Fiore C, D'Errico S, Riezzo I, Fineschi V. Calcium oxalate crystals in acute ethylene glycol poisoning: a confocal laser scanning microscope study in a fatal case. Clin Toxicol (Phila). 2008;46:322-4.
7. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol. 2008;3:208-25.
8. Tobe TJ, Braam GB, Meulenbelt J, van Dijk GW. Ethylene glycol poisoning mimicking Snow White. Lancet. 2002;359:444-5.
9. Megarbane B. Treatment of patients with ethylene glycol or methanol poisoning: focus on fomepizole. Open Access Emerg Med. 2010;2:67-75.
10. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med. 2009;360:2216-23.
11. Fijen JW, Kemperman H, Ververs FF, Meulenbelt J. False hyperlactatemia in ethylene glycol poisoning. Intensive Care Med. 2006;32:626-7.
12. Treichel JL, Henry MM, Skumatz CM, Eells JT, Burke JM. Formate, the toxic metabolite of methanol, in cultured ocular cells. Neurotoxicology. 2003;24:825-34.
13. Desai T, Sudhalkar A, Vyas U, Khamar B. Methanol poisoning: predictors of visual outcomes. JAMA Ophthalmol. 2013;131:358-64.
14. Paasma R, Hovda KE, Jacobsen D. Methanol poisoning and long term sequelae – a six years follow-up after a large methanol outbreak. BMC Clin Pharmacol. 2009;9:5.
15. Hovda KE, Hunderi OH, Rudberg N, Froyshov S, Jacobsen D. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. Intensive Care Med. 2004;30:1842-6.
16. Brent J. Current management of ethylene glycol poisoning. Drugs. 2001;61:979-88.
17. Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol. 1999;37:537-60.
18. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40:415-46.
19. Jacobsen D, McMartin K. Antidotes for methanol and ethylene glycol poisoning. Clin Toxicol. 1997;35:127-43.
20. Beatty L, Green R, Magee K, Zed P. A systematic review of ethanol and fomepizole use in toxic alcohol ingestions. Emerg Med Int. 2013; article ID 638057.
21. McMartin KE, Sebastian CS, Dies D, Jacobsen D. Kinetics and metabolism of fomepizole in healthy humans. Clin Toxicol. 2012;50:375-83.
22. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for Toxic Alcohols Study Group. N Engl J Med. 1999;340:832-8.
23. Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole for the treatment of methanol poisoning. N Engl J Med. 2001;344:424-9.
24. Jacobsen D, Sebastian CS, Blomstrand R, McMartin KE. 4-Methylpyrazole: A controlled study of safety in healthy human subjects after single, ascending doses. Alcohol Clin Expl Res. 1988;12:516-22.
25. Jacobsen D, Sebastian CS, Barron SK, Carriere EW, McMartin KE. Effects of 4-methylpyrazole, methanol/ethylene glycol antidote, in healthy humans. J Emerg Med. 1990;8:455-61.
26. Meulenbelt J, de Vries I, Joore JCA. Behandeling van acute vergiftigingen. Praktische richtlijnen. Houten: Bohn Stafleu van Loghum; 1996.
27. Sturkenboom M, van Rieke H, Uges D. Treatment of ethylene glycol and methanol poisoning: why ethanol? Neth J Crit Care. 2009;13:297-302.
28. Borron SW, Megarbane B, Baud FJ. Fomepizole in treatment of uncomplicated ethylene glycol poisoning. Lancet. 1999;354:831.
29. Hovda KE, Jacobsen D. Expert opinion: fomepizole may ameliorate the need for hemodialysis in methanol poisoning. Hum Exp Toxicol. 2008;27:539-46.
30. Corley RA, McMartin KE. Incorporation of therapeutic interventions in physiologically based pharmacokinetic modeling of human clinical case reports of accidental or intentional overdosing with ethylene glycol. Toxicol Sci. 2005;85:491-501.
31. Lepik KJ, Levy AR, Sobolev BG, et al. Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: a comparison of ethanol and fomepizole. Ann Emerg Med. 2009;53:439-50.
32. Baum CR, Langman CB, Oker EE, Goldstein CA, Aviles SR, Makar JK. Fomepizole treatment of ethylene glycol poisoning in an infant. Pediatrics. 2000;106:1489-91.
33. Benitez JG, Swanson-Biearman B, Krenzelok EP. Nystagmus secondary to fomepizole administration in a pediatric patient. J Toxicol Clin Toxicol. 2000;38:795-8.
34. Boyer EW, Mejia M, Woolf A, Shannon M. Severe ethylene glycol ingestion treated without hemodialysis. Pediatrics. 2001;107:172-3.

35. Brown MJ, Shannon MW, Woolf A, Boyer EW. Childhood methanol ingestion treated with fomepizole and hemodialysis. Pediatrics. 2001;108:E77.

36. Caravati EM, Heileson HL, Jones M. Treatment of severe pediatric ethylene glycol intoxication without hemodialysis. J Toxicol Clin Toxicol. 2004;42:255-9.

37. De Brabander N, Wojciechowski M, De Decker K, De Weerdt A, Jorens PG. Fomepizole as a therapeutic strategy in paediatric methanol poisoning. A case report and review of the literature. Eur J Pediatr. 2005;164:158-61.

38. Detaille T, Wallemacq P, Clement de CS, Vanbinst R, Dembour G, Hantson P. Fomepizole alone for severe infant ethylene glycol poisoning. Pediatr Crit Care Med. 2004;5:490-1.

39. Harry P, Jobard E, Briand M, Caubet A, Turcant A. Ethylene glycol poisoning in a child treated with 4-methylpyrazole. Pediatrics. 1998;102:E31.

40. Hann G, Duncan D, Sudhir G, West P, Sohi D. Antifreeze on a freezing morning: ethylene glycol poisoning in a 2-year-old. BMJ Case Rep. 2012;doi:10.1136.

41. Brent J. Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings. Clin Toxicol (Phila). 2010;48:401-6.

42. Levine M, Curry SC, Ruha A, et al. Ethylene glycol elimination kinetics and outcomes in patients managed without hemodialysis. Ann Emerg Med. 2012;59:527-31.

43. Sivilotti ML, Burns MJ, McMartin KE, Brent J, for the Methylpyrazole for Toxic Alcohols Study Group. Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. Ann Emerg Med. 2000;36:114-25.

44. Dart RC, Caravati EM, McGuigan MA, et al. Medical Toxicology. 3rd ed. Baltimore/London: Lippincott Williams & Wilkins; 2004.

45. Eder AF, McGrath CM, Dowdy YG, et al. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. Clin Chem. 1998;44:168-77.

46. Hovda KE, Andersson KS, Urdal P, Jacobsen D. Methanol and formate kinetics during treatment with fomepizole. Clin Toxicol (Phila). 2005;43:221-7.

47. Palatnick W, Redman LW, Sitar DS, Tenenbein M. Methanol half-life during ethanol administration: implications for management of methanol poisoning. Ann Emerg Med. 1995;26:202-7.