Antidotes for poisoning by alcohols that form toxic metabolites

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The alcohols, methanol, ethylene glycol and diethylene glycol, have many features in common, the most important of which is the fact that the compounds themselves are relatively non-toxic but are metabolized, initially by alcohol dehydrogenase, to various toxic intermediates. These compounds are readily available worldwide in commercial products as well as in homemade alcoholic beverages, both of which lead to most of the poisoning cases, from either unintentional or intentional ingestion. Although relatively infrequent in overall occurrence, poisonings by metabolically-toxic alcohols do unfortunately occur in outbreaks and can result in severe morbidity and mortality. These poisonings have traditionally been treated with ethanol since it competes for the active site of alcohol dehydrogenase and decreases the formation of toxic metabolites. Although ethanol can be effective in these poisonings, there are substantial practical problems with its use and so fomepizole, a potent competitive inhibitor of alcohol dehydrogenase, was developed for a hopefully better treatment for metabolically-toxic alcohol poisonings. Fomepizole has few side effects and is easy to use in practice and it may obviate the need for haemodialysis in some, but not all, patients. Hence, fomepizole has largely replaced ethanol as the toxic alcohol antidote in many countries. Nevertheless, ethanol remains an important alternative because access to fomepizole can be limited, the cost may appear excessive, or the physician may prefer ethanol due to experience.

Introduction

Among the alcohols with a short carbon chain ending with one (alcohol) or two (glycol) hydroxyl groups, there is a subset of compounds that are related by a similar toxic mode of action. While other alcohols such as ethanol and isopropanol produce their toxicity through the alcohol moiety, this subset produces acidic metabolites which are toxic and result in similar clinical features. In this review, this subset is denoted as the metabolically-toxic alcohols and includes ethylene glycol, methanol and diethylene glycol. Some glycol ethers are also metabolized to intermediates, but their poisonings are less severe with few common features, so are not discussed.

The presence of methanol, ethylene glycol and diethylene glycol worldwide in readily available commercial products such as antifreeze, windshield-washer fluid and fuel additives leads to most poisoning cases, often resulting in severe morbidity and mortality. Methanol poisoning is associated with visual disturbances or blindness and with basal ganglion lesions, both can be permanent in survivors [1, 2]. The glycols are associated with acute kidney injury, which can lead to irreversible kidney failure [3–5] and to severe neurological damage [6]. Definitive analytical tests are not readily available and diagnosis is therefore often attempted with imperfect surrogate tests such as osmolar gap and blood gases [7]. Delayed diagnosis and treatment are the main reasons for poor outcomes in these patients that otherwise should have little mortality because early diagnosis normally leads to successful treatment [8, 9]. Hopefully, simpler bedside methods will be available in the near future [10]. The treatment of these poisonings consists of bicarbonate to reverse the metabolic acidosis, alcohol dehydrogenase (ADH) inhibition by either ethanol or fomepizole, and haemodialysis to enhance the elimination of the alcohols and their metabolites. This review will discuss the differing roles of the ADH inhibitors as antidotes for these poisonings, as well as circumstances in which either is used alone or combined with dialysis.
Epidemiology of toxic alcohol ingestions

Poisonings with metabolically-toxic alcohols occur for many reasons, including substitution ingestions due to reduced ethanol availability, suicidal attempts, unintentional ingestions when commercial product is put into other containers or when beverages or medications are illicitly adulterated. Table 1 shows an estimate of the frequency of exposures to these substances for 2013 in the United States National Poison Data System (NPDS) report [11]. These numbers have been relatively stable over the last 20 years based on similar numbers for 1987 [12]. In general, exposures to ethylene glycol are the most common, followed by methanol, with diethylene glycol (as brake fluid) being relatively rare. NPDS data represents reports of ‘exposures’ and may over-report the numbers. Good data on the frequency of these poisonings elsewhere worldwide is not available, although recent outbreaks of methanol poisoning are accessible (http://www.oslo-universitetssykehus.no/omoss_/avdelinger_/akuttmedisinsk_/Documents/outbreaks%20new%20table%20combined.pdf [13]).

**Table 1**


<table>
<thead>
<tr>
<th>Substance</th>
<th>Total exposures</th>
<th>Treated in health care facility</th>
<th>Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>1578</td>
<td>616</td>
<td>8</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>5956</td>
<td>2314</td>
<td>16</td>
</tr>
<tr>
<td>Brake fluid†</td>
<td>882</td>
<td>339</td>
<td>2</td>
</tr>
<tr>
<td>Methanol–1987‡</td>
<td>1601</td>
<td>852</td>
<td>6</td>
</tr>
<tr>
<td>Ethylene glycol–1987‡</td>
<td>4543</td>
<td>1403</td>
<td>11</td>
</tr>
</tbody>
</table>

*Data from the 2013 US National Poison Data System report [11] unless indicated. NPDS report does not produce numbers on DEG directly but brake fluids contain a high concentration of DEG among other solvents. †1987 report for comparison with 2013 numbers [12].

**Mechanisms of toxicity of toxic alcohols**

None of the three compounds is very acutely toxic by itself [32, 33] and they must be metabolized to toxic intermediates, which takes place through oxidations by ADH and aldehyde dehydrogenase (Figure 1). The initial acidic metabolites lead to metabolic acidosis, whereas...
The end metabolites mediate organ damage. Methanol is metabolized to formic acid, which produces acidosis as well as retinal and optic nerve damage [34] leading to blindness observed in methanol poisoning. Ethylene glycol is metabolized to glycolic acid, the major acidic metabolite [35] and then to oxalic acid. The latter combines with calcium to form insoluble calcium oxalate monohydrate (COM) which is deposited in the renal tubules [5] and causes the kidney damage [3]. Diethylene glycol is metabolized to 2-hydroxyethoxyacetic acid (HEAA), which produces the acidosis [36] and then to diglycolic acid, which accumulates in the kidney and is the nephrotoxic metabolite [33, 36]. Because accumulation of metabolites is central to causing toxicity, inhibition of ADH by competitive substrates like ethanol or competitive inhibitors of the enzyme like fomepizole is the primary antidotal treatment for metabolically-toxic alcohol poisonings.

**Treatment criteria**

The traditional threshold for initiating ADH inhibitors is 20 mg dl\(^{-1}\) (3 mmol l\(^{-1}\) ethylene glycol, 6 mmol l\(^{-1}\) methanol), based on anecdotal reports without any apparent justification [37, 38]. The problem with this is that the cut-off for methanol is higher than ethylene glycol, because toxicity will reflect the potential *levels of toxic metabolite* on a molar per molar basis that could be produced from the alcohol. Assuming there is no or only mild metabolic acidosis (base deficit <10 mmol l\(^{-1}\)) and no evidence of organ toxicity on admission, we suggest a cut-off value of 10 mmol l\(^{-1}\) (62 mg dl\(^{-1}\) ethylene glycol, 32 mg dl\(^{-1}\) methanol), which implies 10 mmol l\(^{-1}\) metabolite maximum. The patient should be observed with repeat analysis of acid base every 2 to 4 h to evaluate potential development of metabolic acidosis. Key to this recommendation is that patients will typically not have clinical symptoms with formate <8–10 mmol l\(^{-1}\) [9]. Published data are not available for glycolate but are likely similar or even lower. In addition, if patients have blood concentrations <10 mmol l\(^{-1}\), but have symptoms, they should be treated with antidote according to the other treatment criteria (Table 2).

The applicability of osmolal and anion gaps has been questioned because many conditions can increase the gaps [39–45]. However, Aabakken et al. [46] have identified a reference value for the osmolar gap to be –9 to 19 mOsm kg\(^{-1}\) H\(_2\)O in an emergency department population. By adding a decision level of 25 mOsm kg\(^{-1}\) H\(_2\)O, potential false positives are likely to be excluded [8]. Because methanol or ethylene glycol concentrations <20 mmol l\(^{-1}\) (65 or 110 mg dl\(^{-1}\)) might not increase the osmolar gap above this reference range [8, 46] and
patients who ingested diethylene glycol, treatment with ethanol and haemodialysis was used, albeit with partial success since there was one fatality and two with renal sequelae after 26 months [54]. Even so, one animal study indicates that ethanol treatment can block the acidosis and renal histopathology produced by a large dose of diethylene glycol (16.8 g kg\(^{-1}\)) [55].

Although clinical evidence is lacking for a therapeutic effect of ethanol alone, several studies have demonstrated that ethanol treatment alters the kinetics of toxic alcohols [56, 57]. Because of the extended elimination half-life for the toxic alcohols in patients being treated with ethanol, such studies have led to the recommendation that ethanol therapy needs to be combined with haemodialysis to reduce the length of hospital stay and intensive care time [29].

For therapeutic purposes, a blood ethanol concentration of 100 mg dl\(^{-1}\) (22 mmol l\(^{-1}\)) is usually recommended, but given the dynamic competition for the enzyme, a molar ratio of 1 : 4 for ethanol is likely sufficient to block metabolism [49]. Nevertheless, the ethanol concentration of 100 mg dl\(^{-1}\) has been documented clinically [58] and, since the blood concentration of the metabolically-toxic alcohol is rarely known prior to therapy, an ethanol concentration of 100 mg dl\(^{-1}\) is still the recommended target. A standard regimen for achieving the goal of 100 mg dl\(^{-1}\) would be giving a bolus dose of 0.6 g kg\(^{-1}\) (13 mmol kg\(^{-1}\)), followed by maintenance doses from 66 to 154 mg kg\(^{-1}\) h\(^{-1}\) (1.4 to 3.3 mmol kg\(^{-1}\) h\(^{-1}\)) intravenously or orally (either by drinking or naso-gastric tube), with higher maintenance doses for heavy drinkers (see Table 3 for details) [59]. A convenient formula for calculating the dose in ml of ethanol is:

\[
\text{(dose in mg kg}^{-1}\times 0.127 \times \text{bodyweight in kg)}/\times \%\text{alcohol by volume}
\]

It is critical that the blood ethanol concentration be measured every 1–2 h to allow for changes in the maintenance infusion, but such analyses are often not available. Haemodialysis removes ethanol in the range of 8.9–25 g h\(^{-1}\) [29, 56, 60]. An educated estimate is that the maintenance ethanol dose be doubled during intermittent haemodialysis (see Table 3). Alternatively, adding ethanol to the dialysate has been suggested [61–63], but no published data exist on this. During less effective continuous dialysis techniques, it has been estimated that the ethanol infusion only needs to be increased by about 20% [64].

### Treatment with fomepizole

Fomepizole (4-methylpyrazole (4MP)) is a potent competitive inhibitor of ADH activity with an affinity more
than 1000 times that of the toxic alcohols [65]. Fomepizole was shown to reduce the formation of toxic metabolites in lethal methanol and ethylene glycol poisonings in animal models [66, 67]. In these studies, fomepizole reversed an already-developed metabolite accumulation and severe metabolic acidosis without dialysis. The minimum plasma concentration of fomepizole to prevent accumulation of formate was 10 μmol l⁻¹ [68]. In ethylene glycol-poisoned dogs, fomepizole and ethanol decreased the metabolism of ethylene glycol, but ethanol produced a much greater degree of central nervous system (CNS) depression [69].

The pharmacokinetics of fomepizole has been well characterized in animals and humans. Oral fomepizole is rapidly and completely absorbed in humans; T_max of 2 h and 100% bioavailability [70–72]. Fomepizole is distributed to total body water and is primarily eliminated by metabolism [69, 70]. In human volunteers, elimination of fomepizole after a single IV dose (5 mg kg⁻¹) shows saturation kinetics, with zero order rate of 4.2 μmol l⁻¹ h⁻¹ [71]. Therefore at therapeutic doses producing blood fomepizole concentrations > 10 μmol l⁻¹, fomepizole will have non-linear (“zero order”) elimination kinetics. This has been observed in a methanol-poisoned patient treated with fomepizole (16.9 μmol kg⁻¹ h⁻¹) [73] and in an ethylene glycol-poisoned patient (7.0 μmol kg⁻¹ h⁻¹) [74]. Studies in healthy subjects have indicated that repeated dosing with fomepizole appears to auto-induce its own metabolism after approximately 50 h [71], which is the rationale for the increased fomepizole dose at 48 h.

The dosing schedule for fomepizole is shown in Table 4 [75, 76]. Fomepizole is cleared readily by haemodialysis as shown in animals [77] and poisoned patients [78], so the dosing frequency should be increased during intermittent and continuous haemodialysis (Table 4). Dosing during continuous dialysis can be less frequent due to the apparently lower extraction of fomepizole of 0.08 reported in an unpublished case, compared to 0.71–0.78 with intermittent haemodialysis [79].

### Use of fomepizole and dialysis for methanol poisoning

Methanol is primarily cleared by metabolism, so its half-life during fomepizole therapy is increased (50–80 h) [80]. Haemodialysis is often used to shorten the duration of therapy and hospital stay [81–83], and intermittent haemodialysis has been shown to be superior to continuous dialysis modalities [78]. Previous recommendations used ≥50 mg/dL (15.6 mmol l⁻¹) as a threshold for haemodialysis in fomepizole-treated patients or if the patient displayed visual loss or severe metabolic acidosis [84]. However, it has been suggested [32, 82, 83, 85], and also shown [86], that fomepizole can postpone or ameliorate dialysis and methanol concentrations >50 mg/dL (15.6 mmol l⁻¹) have been successfully treated with only fomepizole [21, 80, 87, 88]. Hence, the use of haemodialysis should depend on the patient condition and not on methanol concentration per se.

### Use of fomepizole and dialysis for ethylene glycol poisoning

Unlike methanol, ethylene glycol is substantially cleared by the kidneys (half-life about 16 h during fomepizole treatment) [21, 87, 88]. Thus, even with metabolic inhibition, most of the ethylene glycol can be eliminated by functional kidneys. Similar to methanol a ≥ 50 mg/dL (8.1 mmol l⁻¹) cut-off has been used for ethylene glycol, but again patients with concentrations above this have been treated with fomepizole alone. There have been
cases with extreme ethylene glycol concentrations (>1000 mg/dL, 161 mmol l\(^{-1}\)), where dialysis was claimed to be needed to avoid complications related to hyperosmolality [89].

**Use of fomepizole for diethylene glycol poisoning**

Fomepizole blocks the acidosis and organ toxicity (liver and kidney) produced by diethylene glycol in rats [47]. There are a small number of reports of successful fomepizole treatment in humans with diethylene glycol poisoning [90–92]. However, treatment of diethylene glycol poisoning is not an FDA-approved indication for fomepizole.

**Comparison of fomepizole and ethanol**

**Efficacy (ability to reverse toxic alcohol effects)**

Both antidotes have a stronger affinity for ADH than the toxic alcohols, but fomepizole has a much higher affinity for the enzyme compared to ethanol (>80 000 versus 10 times stronger than methanol) [93]. Fomepizole binds to the active site competitively, while ethanol itself is metabolized by ADH, thus competes only transiently for the active site. These characteristics favour the efficacy of fomepizole over ethanol. Unfortunately, the prospective clinical trials of fomepizole [75, 76] did not compare it with ethanol and were not able to distinguish the role of antidote therapy from the role of haemodialysis. It is highly unlikely that randomized control trials will be done, because of ethical issues, the infrequency of poisoning and outbreaks, and the lack of facilities for in-depth studies in the developing world where outbreaks usually occur. Comparing survival, either prospectively or retrospectively, between different outbreaks is problematic because of the variable reporting of the number of victims and fatalities, uncertain times from intake to treatment, lack of analytical data, variable toxic alcohol and ethanol concentrations in the toxic liquor and uneven reporting of history of ingestion.

Two large studies have tried to compare the effects of ethanol and fomepizole [94, 95]. Although Paasma and coworkers did not find a significantly better overall outcome with fomepizole, methanol-poisoned patients that could hyperventilate had a significantly better survival with fomepizole compared to ethanol [95]. No difference in outcome between ethanol and fomepizole was found in the study by Zakharov et al. [84], who did a pairwise comparison to evaluate outcome parameters. These patients had similar treatments except for the antidote, supporting ethanol as an equitable antidote given ideal circumstances.

**Efficiency (practicality of use)**

As noted in Table 5, various elements make fomepizole theoretically superior to ethanol in terms of practical use. A major problem with ethanol therapy is the difficulty in maintaining recommended therapeutic concentrations, because of the huge variability in ethanol elimination rates and its rapid elimination during dialysis [96, 97]. Sufficient ethanol concentrations are best maintained by frequent measurements (every 1–2 h) and dose adjustments. However, ethanol analyses need to be available which is not the case in many areas especially the developing world [19]. Zakharov [97] monitored serum ethanol concentrations for 90 ± 20 (SD) hours in 21 methanol-poisoned patients treated with ethanol. Concentrations were in the therapeutic range (100–150 mg/dL, 22–33 mmol l\(^{-1}\)) 28% of the time, above the range 29% of the time (peaking at 350 mg/dL (76 mmol l\(^{-1}\))) and sub-therapeutic 44% of the time.

Another problem with ethanol is the potential for adverse effects, especially CNS depression. In a methanol outbreak, Paasma et al. [15] found that 40% of patients who were awake on admission became comatose within one hour of ethanol treatment. In a retrospective review of adverse events in methanol and ethylene glycol-poisoned cases, CNS symptoms were reported in half of the cases treated with ethanol, while only in 2% treated with fomepizole [98]. Zakharov et al. reported that 48% of patients treated with ethanol developed severe intoxication, but did not become comatose, most likely because of the close monitoring of patients given ethanol [16].

### Table 4

Simplified dosing suggestion for fomepizole treatment for metabolically-toxic alcohol poisonings

<table>
<thead>
<tr>
<th>No dialysis</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>15 mg kg(^{-1}) (Dose 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD [75, 76]</td>
<td>Maintenance dose during IHD</td>
<td>10 mg kg(^{-1}) every 12 h (Dose 2–4)</td>
<td>0.5 mg kg(^{-1}) h(^{-1})</td>
</tr>
<tr>
<td>During dialysis</td>
<td>Maintenance continuous dose during IHD</td>
<td>10 mg kg(^{-1}) every 8 h</td>
<td></td>
</tr>
<tr>
<td>CVVHD (unpublished data)</td>
<td>Maintenance dose during CVVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance continuous dose during CVVHD</td>
<td></td>
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</tr>
</tbody>
</table>

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Although hypoglycemia is a potential risk in children treated with ethanol [98], this has not been observed with toxic alcohol poisoning, most likely because ethanol is infused in a dextrose solution. In a retrospective review of paediatric patients, Roy et al. reported that none had any signs of hypoglycemia and only 16% had a serum glucose concentration between 2.8 and 3.6 mmol L\(^{-1}\) (50 and 65 mg/dL) [99]. Hypoglycemia is not likely with fomepizole [90, 100, 101].

In pregnant women, both ethanol and fomepizole have been used to treat toxic alcohol ingestions [102, 103]. In a study of pregnant rats, no adverse effects to fomepizole were reported [104], and no similar study exists for ethanol. In a pregnant woman with severe metabolically-toxic alcohol poisoning, an antidote is obligatory, and if fomepizole is not available, ethanol should be used.

Although fomepizole is generally well tolerated in humans, occasional adverse effects such as nausea or dizziness have been reported, with uncertain causality. The only contraindication to fomepizole is a previous allergic reaction to methylpyrazoles, although this has not been reported.

**Combination with haemodialysis**

Fomepizole appears to reduce the need for haemodialysis, at least in ethylene glycol exposures. This is because of the well-defined kinetics and simple dosing of fomepizole, allowing haemodialysis to be postponed or omitted in specific cases, particularly if there is limited availability of dialysis [75, 82, 83, 86, 88, 105, 106]. The use of fomepizole simplifies management of many patients, and potentially reduces the use of intensive care beds [14, 15, 19].

**Cost-benefit**

Fomepizole costs more than ethanol in most countries, but an accurate cost comparison needs to include intensive care expenses, need for nursing care and requirement for blood ethanol monitoring [107]. All these costs are country-dependent [108]. The cost of fomepizole therapy may be greater with methanol-poisoned patients than with ethylene glycol-poisoned patients due to the lengthy elimination of methanol during ADH inhibition. In the US and in Norway (personal communication), the costs of ethanol for IV use and of generic fomepizole are similar [32]. Fomepizole is now on the World Health Organisation List of Essential Medicines [109], which is likely to increase the worldwide availability, hopefully to be followed by a lower price.

**Conclusions**

Guidelines suggest that fomepizole should be the main antidote for methanol or ethylene glycol poisoning [37, 38], while ethanol can be used when fomepizole is unavailable. The preference for fomepizole in most countries is based on its efficacy and lower degree of adverse effects compared with ethanol, [95, 108] and its major drawback is the perceived high cost.

**Competing Interests**

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf. Drs. Hovda and Jacobsen declare no support from any organisation for the submitted work. Dr. McMartin had no support form any organization for the submitted work, but reports Other from Mericon Investment group, outside the submitted work. The authors would like to thank Ashton Jorgensen for creating the figure for this manuscript and Yvonne Lao RPh for verifying the dosing recommendations.

**REFERENCES**


