Introduction

Ethanol is the antidote that has been used for poisoning with alcohols since the 1940s [1,2]. Fomepizole is an alcohol dehydrogenase inhibitor. It is used as an antidote for poisoning with ethylene glycol and methanol [3,4]. Lately, fomepizole has been recommended more often than ethanol, because of a supposed better adverse event profile [5-9]. However, it is worth noting that several of those authors are connected with the pharmaceutical industry [5,10-13].

In this review, both antidotes are compared in ethylene glycol and methanol poisoning.

Methanol poisoning

Methanol is used as a solvent for cleaning solutions, dyes, adhesives, thinners, and paint removers. It is widely available as antifreeze, windshield-wiper fluid, and as fuel for camp stoves [1,9]. Methanol is also a cheap substitute of ethanol [1,9].

Methanol itself causes little toxicity [14]. It is metabolized into toxic metabolites, principally in the liver [1]. Alcohol dehydrogenase (ADH) is the primary enzyme responsible for the oxidation of methanol to formaldehyde. Formaldehyde dehydrogenase rapidly converts this into formic acid [1]. Figure 1 shows the metabolism of methanol.

Formic acid is primarily responsible for the metabolic acidosis, visual disturbances (e.g. decreased visual acuity and finally blindness), and mortality associated with methanol poisoning [14,15]. A lethal dose of pure methanol in humans is approximately 1-2 mL/kg [4,15,16].

Ethylene glycol poisoning

Ethylene glycol is used as an unauthorized wine sweetener and is present in coolants and antifreeze [17]. Ethylene glycol poisoning can occur accidentally and intentionally. Doses of 200
mg/kg bodyweight are considered toxic [18]. The lethal dose of ethylene glycol in humans is approximately 1.4 mL/kg [4,9,18]. Ethylene glycol is metabolized more rapidly than methanol [16]. It is metabolized in the liver for approximately 80%. The first step in the metabolism is oxidation to glycoaldehyde by ADH, subsequently to glycolic acid, glyoxylic acid, and oxalic acid (Figure 1). Approximately 20% of ethylene glycol is excreted unchanged by the kidneys [11,18,19]. Ethylene glycol toxicity is complex [6,16]. Glycolic and oxalic acid are the metabolic by-products primarily responsible for the metabolic acidosis and renal damage observed in ethylene glycol poisoning [9]. Oxalic acid binds to calcium, forming insoluble calcium oxalate crystals [18,20]. These crystals deposit in the organs and cause acute renal failure, myocardial dysfunction, neurological dysfunction, and possible pulmonary dysfunction [9].

The elimination of ethylene glycol is more rapid than that of methanol, which means that the latent period for metabolite accumulation to toxic concentrations is usually shorter [16]. Therefore, the start of antidote treatment for ethylene glycol poisoning is more urgent than for methanol.

The treatment of ethylene glycol poisoning consists of administering sodium bicarbonate to counteract the ongoing production of acidic metabolites, administering an antidote to prevent ethylene glycol metabolism, and haemodialysis to remove ethylene glycol and glycolic acid [16,21].

**Ethanol**

As ethanol has been used as an antidote for many decades [1,2], it has never been registered by the pharmaceutical industry. This also implies that a sterile injectable form of ethanol is not commercially available. The efficacy of ethanol as an antidote for toxic alcohol exposure is due to the higher affinity of endogenous ADH for ethanol compared to methanol and ethylene glycol, respectively 10-20 times and 100 times [9,15,18]. This way, ethanol competitively inhibits the metabolism of toxic alcohols to their respective toxic metabolites [4,22]. Ethanol is used as an antidote for poisoning with methanol and ethylene glycol, but also for other alcohol poisonings, like diethylene glycol and propylene glycol [6,9].

Ethanol can be administered either orally or intravenously. Any kind of commercially available ethanol can be used for oral administration. For intravenous administration, ethanol can be infused as a 10% solution in 5% dextrose [15,20]. Ethanol 96% is declared as volume per cent. So, given the specific gravity of ethanol of 0.8, 100 mL ethanol 96% (v/v) contains only 77 g of ethanol [18].

Dose recommendations of ethanol in the treatment of toxic alcohol exposure are divided into a loading dose and a maintenance dose. The loading dose is 600-1,000 mg/kg bodyweight, depending on the blood level of ethanol [15,20]. A maintenance dose is needed to maintain the target ethanol concentration. Individual variability, e.g. chronic alcohol abuse, influences the rate of the ethanol metabolism. The target level of ethanol should be kept between 1000 and 1500 mg/L [15,16,20,23]. This concentration is enough to saturate ADH, thus inhibiting further toxic alcohol metabolism [20].
Haemodialysis eliminates both toxic alcohol and ethanol [16]. Therefore, the maintenance dose of ethanol should be raised by approximately 150 mg/kg/h. The dose recommendations are mentioned in Table 1.

In general, adverse events of ethanol are reported to be central nervous system depression, hypoglycaemia, altered mental status, and possible hepatotoxicity. The advantages of treatment using ethanol are the availability in a clinical setting, and the extensive experience in different toxic alcohol poisonings [1,2,9,16,20,21]. Furthermore, it can be administered both intravenously and orally [9] and it is relatively safe. The disadvantages of treatment with ethanol include a possible altered mental status, dose calculations based on blood-alcohol analysis, and hospitalisation in an ICU during treatment [24].

Fomepizole
Fomepizole or 4-methylpyrazole is a competitive inhibitor of endogenous ADH. Its affinity for the enzyme is approximately 500 to 8000 times higher than that of ethanol [9,22,25]. Fomepizole has been registered in Europe as an antidote for poisoning with ethylene glycol since 2002 [3]. In the United States of America it is also registered for methanol poisoning [2,4].

Fomepizole may be useful in the treatment of poisoning with diethylene glycol and propylene glycol [7,9]. Both alcohols are metabolized by ADH to toxic metabolites. The toxic effects of their metabolites would theoretically be prevented by fomepizole [9].

The efficacy of fomepizole in the treatment of human poisonings derives from retrospective case series, and two prospective clinical trials [5,12,14]. None of the studies involving humans used untreated control subjects or compared fomepizole with ethanol therapy [9,14].

Fomepizole can be given orally, but is only registered as an intravenous preparation [9,26,27]. Like ethanol, fomepizole treatment should be started with a loading dose and continued with a different maintenance dose. The intravenous loading dose is 15 mg/kg. The maintenance dose increases over time. Dose recommendations are mentioned in Table 1. It is advised to maintain fomepizole treatment until the methanol or ethylene glycol levels have been reduced to 200 mg/L or lower [1,3,4,14-16,22,28]. The increase in fomepizole dosing is due to the auto-inducing activity of fomepizole on cytochrome P450 2E1 [1,14,22,25].

Fomepizole has negligible protein binding and is therefore removed almost completely by haemodialysis. The dosing of fomepizole should be increased to every four hours or should be a continuous infusion of 1 mg/kg/h during haemodialysis [1,3,4,7,14,26]. Indications for haemodialysis in patients treated with fomepizole are considered to be persistent metabolic acidosis, renal impairment or clinical deterioration despite treatment [8,15,18].

Fomepizole is not officially approved for use in children [23]. No controlled studies have been conducted [23]. However, several children have been treated with fomepizole, either alone or after a loading dose of ethanol [23,29]. One patient experienced a transient episode of hypoglycaemia. This 22-month-old child received only fomepizole [29]. No major complications were reported [29].

Table 1. Dose recommendations for ethanol and fomepizole [1,3,4,7,15,18,26].

<table>
<thead>
<tr>
<th>ETHANOL</th>
<th>FOMEPIZONE</th>
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<tbody>
<tr>
<td><strong>Loading dose:</strong></td>
<td>D_l = V_d x B_w (C_t - C_m)</td>
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<tr>
<td>D_l = loading dose [mg]</td>
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<tr>
<td>V_d = volume of distribution [male 0.7 L/kg, female 0.6 L/kg]</td>
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<tr>
<td>B_w = body weight [kg]</td>
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<tr>
<td>C_t = target concentration ethanol [mg/L]</td>
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<tr>
<td>C_m = measured concentration ethanol [mg/L]</td>
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<tr>
<td>D_l = loading dose [mg]</td>
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<tr>
<td>B_w = body weight [kg]</td>
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<tr>
<td><strong>Maintenance dose:</strong></td>
<td>D_m = C_t x V_max x B_w / (K_m + C_t)</td>
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<tr>
<td>D_m = maintenance dose [mg/h]</td>
<td></td>
</tr>
<tr>
<td>V_max = maximum enzyme capacity [mg/kg.h]</td>
<td></td>
</tr>
<tr>
<td>K_m = Michaelis-Menten-constant [138 mg/L]</td>
<td></td>
</tr>
<tr>
<td>D_m = maintenance dose [mg/12h]</td>
<td></td>
</tr>
<tr>
<td>D_m = maintenance dose, after 60h [mg/12h]</td>
<td></td>
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<tr>
<td><strong>Maintenance dose during haemodialysis:</strong></td>
<td>D_m [haemodialysis] = D_m + (C_x x B_w)</td>
</tr>
<tr>
<td>D_m = maintenance dose during haemodialysis [mg/h]</td>
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</tr>
<tr>
<td>C_x = variable, dependent on artificial kidney and blood flow [mg/kg.h]</td>
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</tr>
<tr>
<td>D_m = maintenance dose during haemodialysis [mg/4h]</td>
<td></td>
</tr>
<tr>
<td>D_m = maintenance dose during haemodialysis, after 60h [mg/4h]</td>
<td></td>
</tr>
<tr>
<td>D_m = maintenance dose during haemodialysis [mg/h]</td>
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</tbody>
</table>
The advantages of treatment with fomepizole are supposed to be its minimal adverse events [25]. The most common adverse effect is a burning feeling at the infusion site. Headache, nausea, dizziness, agitation, eosinophilia, and seizures have also been reported. It is unknown whether these side effects are related to fomepizole treatment or caused by the toxic alcohols [14]. A case of serious adverse events such as hypotension and bradycardia, was recently reported [30].

Contrary to ethanol, dose calculations based on serum levels are not needed for fomepizole, resulting in an easier administration scheme.

The disadvantages of fomepizole are the high costs, combined with its limited shelf life, the low availability and the fact that it is only registered for ethylene glycol poisoning in Europe [3,9,11,15,31,32].

**Haemodialysis**

The indications for haemodialysis in toxic alcohol poisoning are severe metabolic acidosis, deteriorating vital signs despite supportive care, renal failure, and electrolyte imbalances unresponsive to therapy [9,11,20,26,33]. Haemodialysis should also be considered if methanol or ethylene glycol levels are above 500 mg/L [7,9,34,35].

Haemodialysis is very effective in removing toxins from the blood. In case of ethylene glycol poisoning, unmetabolized ethylene glycol, glycolic acid, and calcium oxalate are eliminated [9,11,20,28]. In methanol poisoning, methanol and formate are removed [1,26,28,36,37]. Haemodialysis is also helpful in correcting the metabolic imbalance [9,11,20,26].

An advantage of fomepizole may prove to be the capability of eliminating the need for haemodialysis in certain patient groups [8,10,13,20,26,29,31,33,36]. Fomepizole, like ethanol, only inhibits the metabolism of ethylene glycol or methanol [21]. When ethanol or fomepizole are administered and renal failure is present, haemodialysis is the only method for the removal of ethylene glycol [20]. Furthermore, haemodialysis not only removes the parent compound and its toxic metabolites, but also corrects the metabolic imbalance [9]. Kraut et al. state that controlled, prospective studies are useful to decide whether fomepizole will be able to obviate the need for haemodialysis [9].

It has been suggested that patients with normal renal function may survive on fomepizole treatment alone [11,33]. Twenty percent of ethylene glycol is excreted unchanged in the urine [11,19], Fomepizole may reduce the need for haemodialysis, if the metabolism of ethylene glycol is fully inhibited by the antidote and ethylene glycol itself is completely eliminated [16]. However, inhibiting the metabolism by antidotal treatment and inhibiting excretion by the commonly observed renal failure reduces the endogenous elimination of ethylene glycol to a minimum [16]. Thus haemodialysis becomes the major way to remove ethylene glycol and its metabolites from the body [16]. Without haemodialysis, the duration of the fomepizole treatment will therefore increase. Furthermore, any metabolite formed before treatment will remain toxic, because it is not removed.

**Discussion**

Its high affinity for ADH is stated as an advantage of fomepizole [9]. This only means that a lower concentration of fomepizole is required compared to ethanol and shows that both antidotes target the same mechanism.

Fomepizole is thought to be easier to administer, as dose calculations are based on body weight rather than on serum levels. It could be argued that it would be more elegant to dose fomepizole on its serum level, because of the auto-inducing activity of fomepizole. Furthermore, this does not eliminate the need for alcohol analyses, as these are still indicated to control the blood levels of the toxic alcohols during fomepizole treatment [3,4].

Some experts consider a suspicion of methanol or ethylene glycol ingestion sufficient to start fomepizole [10]. It is obvious that we do not agree.

Kraut et al. state that the increase in serum osmolality is a disadvantage of ethanol treatment, as this would complicate the monitoring response [9]. We do not agree. As we argued before, serum osmolality is unreliable in toxic alcohol poisoning.

Extensive experience with ethanol in different alcohol poisonings has demonstrated that ethanol is highly effective as an antidote [1,2,9,16,20].

In general, the adverse events of ethanol are reported to be central nervous system depression, hypoglycaemia, altered mental status, and possible hepatotoxicity. However, there is limited information about the adverse effects of ethanol when used as an antidote [1,2,5,11,26]. The altered mental status due to the administered ethanol should be considered relative to the other toxic alcohols consumed and to the patients who may be used to levels that exceed the target level. It goes without saying that the latter is not true for children or unintentional alcohol poisonings.

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**Table 2. The differences between ethanol and fomepizole.**

<table>
<thead>
<tr>
<th></th>
<th>ETHANOL</th>
<th>FOMEPIZOLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Available in clinical setting</td>
<td>Minimal adverse effects</td>
</tr>
<tr>
<td></td>
<td>Extensive experience in the Netherlands</td>
<td>Registered for ethylene glycol poisoning</td>
</tr>
<tr>
<td></td>
<td>Antidote in different alcohol poisonings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Administration orally and intravenously</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Dose calculations based on blood-alcohol levels</td>
<td>High costs</td>
</tr>
<tr>
<td></td>
<td>Hospitalization in intensive care unit</td>
<td>Not available in all clinical settings</td>
</tr>
<tr>
<td></td>
<td>necessary during treatment</td>
<td>Limited shelf life</td>
</tr>
<tr>
<td></td>
<td>Not officially registered as antidote</td>
<td>Not registered for methanol in the Netherlands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of experience in the Netherlands</td>
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<td></td>
<td></td>
<td>Little experience in other alcohol poisonings</td>
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</table>
Experience with fomepizole in children is limited. Therefore, there can be no preference for the time being. However, it may be anticipated that this patient group may benefit from the newer antidote in the future, as these patients may be more susceptible to the altered mental status caused by ethanol.

In our opinion, the need for haemodialysis should be considered in the same way for both fomepizole and ethanol, because both antidotes only affect the metabolism of the ingested substance and not the elimination of its metabolites. Without haemodialysis, the duration of the fomepizole treatment will increase. Any metabolite formed before treatment will remain toxic, because it is not removed. We agree with Kraut et al. [9] that controlled, prospective studies are needed before it is possible to conclude that fomepizole obviates the need for haemodialysis.

Intravenous treatment with 96% sterile ethanol for 60 hours costs approximately € 20. The treatment of ethylene glycol or methanol poisoning with fomepizole is far more expensive than with ethanol. One phial of fomepizole 100 mg (5 mg/mL, 20 mL) costs approximately € 110. A loading dose of 15 mg/kg costs approximately € 1,100. If five doses (treatment 48 hours) are needed, the treatment cost will amount to approximately € 4,300. In the case of haemodialysis, the costs will even be higher. Fomepizole is dialyzable and therefore the frequency of dosing should be increased to every four hours during haemodialysis. So ethanol may be preferred, especially if resources are limited [21].

Table 2 reflects our point of view on the differences between ethanol and fomepizole.

### Conclusion

In the Netherlands, in our opinion, ethanol still is the antidote of choice for poisoning with ethylene glycol or methanol, because of the extensive experience and the constant availability of the antidote. Furthermore, both gas chromatography for blood-alcohol analysis and haemodialysis are commonly available in most Dutch hospitals.

It is our opinion that the minimal adverse effects of fomepizole do not justify the high costs of its treatment, whilst its low availability due to costs and limited shelf life is also problematic.

In conclusion, ethanol can treat toxic alcohol poisonings safely and effectively.

### References


