## Fomepizole versus Ethanol for treating toxic alcohol poisoning

### QUESTION

Should adults/children with toxic alcohol poisoning be treated with fomepizole compared to ethanol?

### CONTEXT

**Toxic alcohol poisoning**

Alcohol-related intoxications, including methanol, ethylene glycol, diethylene glycol, propylene glycol, and alcoholic ketoacidosis can present with a high anion gap metabolic acidosis and increased serum osmolal gap, whereas isopropanol intoxication presents with hyperosmolality alone. The effects of these substances, except for isopropanol and possibly alcoholic ketoacidosis, are due to their metabolites, which can cause metabolic acidosis and cellular dysfunction.

Poisoning with ethylene glycol or methanol can occur through attempted inebriation, unintentional ingestion, or intentional self-harm. Ethylene glycol is a component of antifreeze, which is the major source of exposure in poisonings. Antifreeze generally has a bright color, and its ethylene glycol content confers a sweet taste. These qualities render it a common source of pediatric ingestions. The principal clinical features of ethylene glycol poisoning are some degree of inebriation or alteration in consciousness, a profound metabolic acidosis, oxalate crystalluria, and acute renal failure. In severe cases, clinical hypocalcemia, multiorgan-system failure, and death occur.

On the other hand, methanol poisoning most often occurs from the ingestion of windshield-washer fluid. Methanol is also used in copy machines and as an ingredient in canned heating products, embalming fluids, and paint removers. Methanol poisoning is a well-known consequence of ingesting “moonshine” liquor. The ingestion of small quantities of methanol induces a profound metabolic acidosis, visual changes that may progress to blindness, and (in severe cases) multiorgan-system failure and death. Untreated methanol poisoning is associated with a rate of death of 28%.

Traditional treatment of toxic alcohol poisoning consists of sodium bicarbonate, ethanol, and hemodialysis. However, fomepizole is a new agent with a specific indication by the U.S. Food and Drug Administration for the treatment of ethylene glycol poisoning. Ethanol and fomepizole are thought to act as inhibitors of alcohol dehydrogenase and therefore prevent the formation of acidic ethylene glycol metabolites.

### INTERVENTION

**Fomepizole**

#### Survival

A high rate of patients (age ≥12) treated with fomepizole (loading dose IV: 15 mg/kg, followed by 10 mg/kg every 12 hours for 48 hours, plus 15 mg/kg every 12 hours) survived after an ethylene glycol poisoning. Similar results regarding methanol poisoning were found. *Low quality evidence*

#### Adverse events

A low rate of adverse events is associated to fomepizole compared to treatment with ethanol in paediatric patients with toxic alcohol poisoning (ethylene glycol and methanol poisoning). *Low quality evidence*
Summary of the Evidence

**Benefits**

Two prospective observational studies were located related to use of fomepizole in toxic alcohol poisoning. The first study, enrolled 19 patients (age≥12) with ethylene glycol poisoning who were administered IV fomepizole (loading dose 15 mg/kg, followed by 10 mg/kg every 12 hours for 48 hours) [1]. Thereafter, the dosage was increased to 15 mg/kg every 12 hours to adjust for increased fomepizole metabolism. Nine of 19 patients (47%) had high serum creatinine concentrations, and 15 (79%) had metabolic acidosis at enrollment. The serum creatinine concentration normalized during treatment in 6 of 9 patients (67%) with renal dysfunction. The 10 patients with normal serum creatinine concentrations at enrollment had no change in renal function. Seventeen patients underwent hemodialysis. One patient with extreme acidosis died, while the remaining 18 patients survived their acute illness uneventfully.

In the second study, 11 patients (age≥12) with methanol poisoning were enrolled [2]. The treatment protocol consisted of the administration of fomepizole, with the intravenous infusion of glucose, electrolytes, and fluids, as clinically indicated. Nine patients survived even though several of them were initially comatose with pH levels as low as 6.90, plasma methanol concentrations as high as 612 mg per deciliter (191.0 mmol per liter), and visual deficits severe enough that they were only able to count fingers. All these patients regained their baseline visual acuity. In contrast to the two patients who died, all survivors had plasma formic acid concentrations of no more than 100 mg per deciliter (21.7 mmol per liter).

**Risks**

One recent cohort study of adverse events associated with antidotes ethanol and fomepizole in methanol or ethylene glycol poisonings was located [3]. Two hundred twenty-three charts of patients aged 13 years or older were reviewed and 172 analyzed. Toxicologists identified at least 1 adverse drug event in 74 of 130 (57%) ethanol-treated and 5 of 42 (12%) fomepizole-treated cases. Central nervous system symptoms accounted for most adverse drug events (48% ethanol-treated, 2% fomepizole-treated). Severe adverse drug events occurred in 26 of 130 (20%) ethanol-treated (coma, extreme agitation, cardiovascular) and 2 of 42 (5%) fomepizole-treated (coma, cardiovascular). Serious (life-threatening) adverse drug events occurred in 11 of 130 (8%) ethanol-treated (respiratory depression, hypotension) and 1 of 42 (2%) fomepizole-treated (hypotension, bradycardia) cases.

Median adverse drug event onset was within 3 hours after the start of either antidote. Ethanol and fomepizole adverse drug event rates were 0.93 and 0.13 adverse drug events per treatment-day, respectively. Adjusted hazard ratio was 0.16 (95% confidence interval 0.06, 0.40).

**Applicability**

No studies comparing ethanol with fomepizole in toxic alcohol poisoning were found. Most of the evidence supporting the use of both fomepizole and ethanol is derived from several case reports and retrospective case series without control group. No children were included in these reports (age less than 12 years).

The results of these observational studies suggest a benefit related to use of fomepizole in treatment of toxic alcohol poisoning of patients aged 12 years of older.

**Commentaries**

The American Academy of Clinical Toxicology has promulgated practice guidelines for the treatment of ethylene glycol [4] or methanol poisoning [5]. These guidelines call for fomepizole to be the first-line agent in the treatment of both types of poisoning, with ethanol to be used if fomepizole is unavailable. Evidence for pediatric patients is not available.

**Costs**

We did not identify economic assessments related to either fomepizole or ethanol cost in toxic alcohol poisoning.

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of Evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Direct Evidence</th>
<th>Size of Effect</th>
<th>GRADE</th>
<th>Comments</th>
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<td>1 (19)</td>
<td>Survival</td>
<td>Fomepizole in ethylene glycol poisoning</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>Very low</td>
<td>The major limitation to this study was that there was no control group.</td>
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<tr>
<td>1 (11)</td>
<td>Survival</td>
<td>Fomepizole in methanol poisoning</td>
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<td>Very low</td>
<td>The major limitation to this study was that there was no control group.</td>
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<td>Adverse events</td>
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<td>0</td>
<td>0</td>
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</table>

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytic studies / Expert opinion