

REVIEW

# Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings

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**Introduction.** The use and clinical efficacy of the alcohol dehydrogenase inhibitor fomepizole is well established for the treatment of ethylene glycol and methanol poisonings in adults. **Methods.** A computerized search of the U.S. National Academy of medicine and EMBase databases was undertaken to identify published cases of patients treated with fomepizole. This search strategy identified 14 published cases related to the topic of this review: 10 due to ethylene glycol poisoning, 1 due to diethylene glycol poisoning, 1 due to butoxyethanol ingestion, and 2 due to methanol poisoning. The median age of these cases was 5.5 years old. **Fomepizole in glycol and glycol ether poisoning.** For the 10 ethylene glycol poisoned patients, the median recorded values of their arterial pH was 7.27 (range 7.03–7.38), serum bicarbonate concentration was 13 mEq/L (range 2–25), and ethylene glycol concentration was 2,140 mg/L (range 130–3,840). Eight of these patients were not hemodialyzed. The eight patients who were not hemodialyzed had ethylene glycol concentrations as high as 3,500 mg/L and serum bicarbonate concentrations as low as 4 mEq/L. All 10 patients had resolution of their metabolic acidosis and recovered without sequelae. The half-times of ethylene glycol elimination ranged from 9 to 15 h during fomepizole therapy, which is faster than the 19.7 h reported in adults. The two patients who ingested diethylene glycol or butoxyethanol all recovered without sequelae. The patient who ingested the butoxyethanol had a serum bicarbonate concentration of 13 mEq/L and was not hemodialyzed. **Fomepizole in methanol poisoning.** One of the two children who ingested methanol was hemodialyzed. Both cases had a similar degree of severity. **Does fomepizole obviate the need for hemodialysis?** Based on the experience reviewed herein it appears that, as in adults, hemodialysis may not be necessary in most cases of pediatric ethylene glycol poisoning if treated with fomepizole. **Fomepizole pharmacokinetics.** Plasma fomepizole concentrations were measured in three cases and were found to be therapeutic with apparent Michaelis–Menton kinetics, having a zero-order elimination rate of 0.6–1 mg/L/h at higher concentrations and a first-order elimination with an apparent elimination half-time of 3.9 h at lower concentrations. **Fomepizole regimen.** Most cases used the current U.S.-approved regimen. **Adverse effects of fomepizole.** The one adverse effect reported during fomepizole therapy was transient nystagmus in a 6-year-old with a serum ethylene glycol concentration of 130 mg/L and a serum bicarbonate concentration of 2 mEq/L; it is likely that ethylene glycol itself was the cause. **Comparison of fomepizole with ethanol therapy.** Two cases were originally treated with ethanol but switched to fomepizole because of adverse effects. In both cases, the adverse reactions to ethanol resolved once fomepizole treatment was initiated. **Conclusions.** The limited data available suggest that fomepizole, using the same dosage regimen as that used for adults, is efficacious and well tolerated in pediatric patients. In many cases of pediatric ethylene glycol poisoning treated with fomepizole, hemodialysis may not be necessary despite high concentrations and the presence of metabolic acidosis.

**Keywords** Fomepizole; Ethylene glycol; Diethylene glycol; Butoxyethanol; Methanol; Poisoning; Children

## Introduction

The contemporary mainstay in the treatment of ethylene glycol and methanol poisonings is the inhibition of alcohol dehydrogenase, preferably by fomepizole.<sup>1</sup> Hemodialysis may be added to the therapeutic approach to these poisonings in selected cases, more so for those treated with ethanol than with fomepizole.<sup>1–3</sup> However, the clinical trials<sup>4,5</sup> and case series<sup>6–8</sup> which constitute most of the published experience

with fomepizole is based on adult patients. In adults, fomepizole has been shown to be extremely well tolerated with a minimum of adverse reactions.<sup>1,4–8</sup>

There have been no formal studies on the inhibition of alcohol dehydrogenase in the treatment of methanol or ethylene glycol poisoning, by either fomepizole or ethanol, in the pediatric population. As described below, the ken of the published English language experience with fomepizole in pediatric patients identified by the author is limited to 14 cases comprised of 9 individual case reports<sup>9–17</sup> and one series<sup>1</sup> of 5 patients (Table 1).

The purpose of this short review is to compile the information obtained from this published experience and to highlight the need for further studies on this topic in pediatric patients. Because of the limited body of data that can be extracted and

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**Table 1.** Reported cases of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings treated with fomepizole

Reference	Number of cases	Age	Substance ingested	Initial bicarbonate concentration (mEq/dL)	Initial serum/plasma concentration (mg/L) of ingested substance	Initial pH	HD <sup>a</sup>	T <sub>1/2</sub> (h) <sup>b</sup>	Sequelae	Adverse events reported as related to fomepizole therapy <sup>c</sup>
Caravati <sup>18</sup>	5	22 months–13 years	Ethylene glycol	4–14	1,130–3,040	NR	No	10–15 <sup>d</sup>	None	None reported
Detaille <sup>9</sup>	1	5 months	Ethylene glycol	11.1	3,500	Not done	No	11	None	None reported
Boyer <sup>10</sup>	1	13 years	Ethylene glycol	25	1,030	7.38	No	Not reported	None	None reported
Baum <sup>11</sup>	1	8 months	Ethylene glycol	17.5	3,840	7.32	Yes	9	None	None reported
Benitez <sup>12</sup>	1	6 years	Ethylene glycol	2	130	7.03	Yes	Not reported	None	Transient nystagmus
Harry <sup>13</sup>	1	4 years	Ethylene glycol	10.7	3,100	7.29	No	10	None	None
Brophy <sup>14</sup>	1	17 months	Diethylene glycol	26	17	Not reported	Yes	Not reported	None	None
Osterhaut <sup>15</sup>	1	16 years	Butoxyethanol	13	Not reported	Not reported	No	Not reported	None	None reported
Brown <sup>16</sup>	1	5 years	Methanol	23	350	7.43	Yes	Not reported	None	None reported
DeBrabander <sup>17</sup>	1	3 years	Methanol	22	290	7.34	No	Not reported	None	None reported

<sup>a</sup>Hemodialysis.

<sup>b</sup>As reported in the publication under conditions of alcohol dehydrogenase inhibition by fomepizole while not undergoing hemodialysis.

<sup>c</sup>None: There was an explicit statement indicating that there were no adverse effects attributed to fomepizole. None reported: There were no adverse effects described that were attributed to fomepizole.

<sup>d</sup>Estimated.

critically assessed from abstracts, this review will be limited to a discussion of fully published cases.

## Methods

A computerized search of the U.S. National Academy of medicine and EMBASE databases was undertaken using the search terms fomepizole or 4-methylpyrazole and therapeutic use to identify published cases of patients treated with fomepizole. These were screened and all reports in patients under 18 years old were retained for abstraction. The references in all these cases, and a further search for any publications citing the retained cases, were also undertaken to identify any reports that may have been overlooked in the initial search. Lastly, the author's large personal files on fomepizole, ethylene glycol, and methanol were searched. This total search strategy identified the 14 published cases related to the topic of this review.

## Use of fomepizole in children

The 14 published cases range from 5 months to 16 years old, with a median of 5.5 years. In 10 cases the fomepizole was given because of ingestion of ethylene glycol,<sup>9-13,18</sup> methanol was ingested in 2,<sup>16,17</sup> and there was 1 case of butoxyethanol<sup>15</sup> and 1 case of diethylene glycol ingestion<sup>14</sup> (Table 1).

### Ethylene glycol poisoning

Of the 10 patients with ethylene glycol poisoning, the initial arterial pH, reported in 5, ranged from 7.03 to 7.38 (median 7.27). Their median serum bicarbonate concentration, reported in all cases, was 13 mEq/L (range 2–25). The measured median serum ethylene glycol concentration reported at presentation for all 10 cases was 2,140 mg/L (range 130–3,840). Hemodialysis was utilized in only 2 of the 10 patients. The eight patients that were not hemodialyzed had a median serum ethylene glycol concentration of 2,160 mg/L (range 1,030–3,500) and median serum bicarbonate concentration of 13 mEq/L (range 4–25). The lowest measured arterial pH in the nonhemodialyzed patients was 7.29, although this value was reported in only one half of the cases. Nine of the 10 cases presented with a metabolic acidosis. In all of these patients, the acidosis resolved once fomepizole therapy was initiated. All 10 patients survived with no adverse sequelae described.

Thus, it appears, based on this limited experience, that pediatric patients with serum ethylene glycol concentrations well in excess of those that would be a trigger for hemodialysis if ethanol treated<sup>2</sup> may be treated with fomepizole alone, even in the presence of some degree of metabolic acidemia.

The reported half-times of ethylene glycol elimination in fomepizole-treated nonhemodialyzed pediatric patients,

given in eight reports,<sup>9,11,13,18</sup> ranged from 9 to 15 h, which is faster than the 19.7 h observed in adults in the META trial.<sup>4</sup> This close clustering of half-times occurred despite the range of ages of 5 months to 13 years in those patients in whom it was reported.

### Poisoning by other glycols

There were two cases reported: one was a 17-month-old who ingested diethylene glycol, was not acidotic (serum bicarbonate concentration of 25 mEq/L), whose diethylene glycol concentration was 17 mg/L, but was hemodialyzed<sup>14</sup>; the second was a 16-year-old who ingested butoxyethanol and had an initial serum bicarbonate concentration of 13 mEq/L.<sup>15</sup> Both patients recovered without sequelae or any adverse effects.

### Methanol poisoning

The two reported cases of methanol poisoning were in a 3- and a 5-year-old.<sup>16,17</sup> They had serum bicarbonate concentrations of 22 and 23 mEq/L, plasma methanol concentrations of 290 and 350 mg/L, and arterial pHs of 7.34 and 7.43, respectively (Table 1). Despite similar ages and presentations, one was hemodialyzed and the other was not. Both recovered without reported sequelae and did not have any reported adverse effects of fomepizole administration. In neither case was the elimination rate during fomepizole therapy in the absence of hemodialysis given.

## Does fomepizole obviate the need for hemodialysis?

Pediatric patients who are significantly acidotic, with serum bicarbonate concentration as low as 4 mEq/L,<sup>18</sup> and have ethylene glycol concentrations up to 3,500 mg/L<sup>9</sup> have been effectively treated with fomepizole in the absence of hemodialysis. This suggests that in pediatric patients hemodialysis may be foregone in many cases, similar to what has been observed in adults. The fact that ethylene glycol appears to have a more rapid elimination in the pediatric population treated with fomepizole than in adults provides further support for withholding hemodialysis when renal function is intact. Hemodialysis, or other extracorporeal techniques, carries a risk of infection, air embolism, thrombosis, hypovolemia, hypotension, and electrolyte abnormalities. These techniques can be especially challenging in infants. Thus, there are substantial benefits to avoiding using extracorporeal techniques, especially in children. Doing so should also reduce the cost of hospitalization for patients with ethylene glycol poisoning and normal renal function because this substance is rapidly cleared through the kidney. However, because the data reviewed above are largely anecdotal, it is important for further research and clinical experience to be published on the issue of fomepizole administration in children and the foregoing of hemodialysis.

In contrast to ethylene glycol, methanol elimination under conditions of alcohol dehydrogenase inhibition is slow.<sup>5</sup> Thus, extracorporeal techniques may be warranted if plasma methanol concentrations are substantially elevated (e.g., over 500 mg/L).<sup>3</sup>

### Fomepizole pharmacokinetics in children

The pharmacokinetics of fomepizole elimination was studied in a 5-month-old child who ingested ethylene glycol<sup>9</sup> and was treated by the standard protocol of a loading dose of 15 mg of fomepizole/kg followed by 10 mg/kg at 12 h intervals. The analysis found that the mean peak plasma concentration after each fomepizole dose was  $18.9 \pm 2.2$  mg/L. In this single case, plasma fomepizole concentrations ranged from 4.5 to 21 mg/L, all of which are well above the therapeutic target of 0.74 mg/L.<sup>19</sup> The apparent half-time of plasma fomepizole elimination decreased from 12.3 to 3.9 h as fomepizole concentrations declined, suggesting a change from zero- to first-order elimination kinetics. The zero-order component appeared to have an elimination rate of 0.6–1 mg/L/h, after which there was a transition to first-order kinetics with an elimination half-time of 3.9 h. This is faster than the elimination rate of 0.3 mg/L/h observed by Jacobsen et al.<sup>20</sup> in human volunteers. However, despite this faster elimination the fomepizole concentration remained therapeutic throughout this child's entire course. Thus, the current regimen used in adults appeared, both on the basis of clinical experience and pharmacokinetics, to work well in this case study.

Plasma fomepizole concentrations were also determined by Harry et al.<sup>13</sup> in a 4-year-old child 2 h after each of three infusions and were found to be 18.5 mg/L following the 15 mg/kg loading dose and 17.5 and 12.5 mg/L after each of two 10 mg/kg doses. Based on the pharmacokinetics of fomepizole in adults,<sup>5,20</sup> and in the pediatric kinetic data by Wallemacq et al.<sup>19</sup> the plasma concentrations determined by Harry et al.<sup>13</sup> should remain well over the therapeutic threshold for the entire 12 h interdosal period.

### Fomepizole regimen in children

Therapeutic plasma fomepizole concentrations have been reported to be achieved using the dosing regimen that has been validated for adults.<sup>5</sup> In contrast, maintaining target blood ethanol concentrations, taken here as the generally accepted value of at least 1,000 mg/L, appears to be challenging in the pediatric population. In the study of Roy et al.,<sup>21</sup> mean ethanol concentrations were subtherapeutic by this criterion. The degree of efficacy of ethanol, if any, at lower than 1,000 mg/L is unknown.

The currently accepted regimen for use of fomepizole<sup>1</sup> appears to be appropriate for pediatric patients as well. However, plasma fomepizole concentrations were only determined in three cases,<sup>9,13,19</sup> all of which found them to be well above the lower limit of the target values for efficacy. Although

plasma fomepizole concentrations were not determined in the other patients, the fact that there was no treatment-emergent development, or worsening, of metabolic acidemia provides strong indirect evidence that acidic metabolites of ethylene glycol and methanol were not being formed to any clinically detectable degree and thus alcohol dehydrogenase was effectively inhibited. In fact, in all cases acid–base disturbances resolved after the initiation of fomepizole therapy.

### Adverse effects of fomepizole

Similar to the experience with adults<sup>1,4–8</sup> there appeared to be few adverse effects associated with fomepizole administration in these pediatric patients. One case of nystagmus was reported in a 6-year-old with ethylene glycol poisoning. However, it is unclear whether that was related to fomepizole because this patient had multiple metabolic abnormalities, had received at least cefotaxime, pyridoxine, thiamine, and did not develop the nystagmus until 2 h after the fomepizole administration. It is probable that ethylene glycol itself was the cause as this has been reported previously.<sup>2</sup> The nystagmus resolved 1 h later without any reported sequelae.<sup>12</sup> No other adverse effects were reported.

### Comparison of fomepizole with ethanol therapy

There have been no clinical trials, in adults or in pediatrics, comparing the efficacy and safety of fomepizole versus ethanol. However, the adverse effect profile for ethanol is well known<sup>1,22</sup> and contrasts with the benign side effects reported for fomepizole. In a recent retrospective cohort study of 172 patients at least 13 years old, ethanol was found to have a significantly worse side effect profile than fomepizole, with an adjusted hazard ratio for fomepizole-related adverse effects (compared to ethanol) of 0.16 (95% confidence interval of 0.06–0.40).<sup>23</sup>

Children presenting for medical care related to ethanol ingestion/intoxication have been reported in several case series and hypoglycemia was a documented adverse effect.<sup>24,25</sup> Thus, hypoglycemia is one potential adverse effect of particular interest during ethanol therapy of patients. However, it is unlikely that this would be a major problem in appropriately medically managed children because they would be expected to be simultaneously receiving intravenous glucose.

A valiant attempt to assess the potential adverse effects of ethanol therapy, published in this journal, was undertaken by Roy et al.<sup>21</sup> who reported on a retrospective chart review of 60 patients aged 6 months to 18 years treated with ethanol for suspected methanol poisoning. Six (10%) of these patients developed drowsiness after ethanol administration, none requiring intubation. No other major adverse effects were reported; however, 16% of the cases developed asymptomatic hypoglycemia. The lack of adverse events in the Roy et al.<sup>21</sup> study may have been related to the intravenous dextrose that

was administered to 83% of the patients and the relatively low measured serum ethanol concentrations (means 750–830 mg/L in the various subgroups reported).

The pediatric experience from which we may get a glimpse of the possible comparative effects of these two antidotes derives from two anecdotal cases, both of which document an adverse reaction to ethanol that resolved when fomepizole was substituted.

Boyer et al.<sup>10</sup> describe a 13-year-old girl who purposely ingested ethylene glycol, was treated with ethanol, “promptly became obtunded,” required endotracheal intubation for airway protection, was transferred to a tertiary care center, had treatment switched to fomepizole, and “was extubated and transferred to a medical floor approximately 12 h after arrival.” The time frames and the laboratory studies at the initial hospital – the latter showing that a metabolic acidosis had not yet developed – both strongly suggest that the observed sequence of events was not due to the ethylene glycol but to the antidotes administered, characterized by a detrimental effect from ethanol which resolved after fomepizole was substituted.

A similar experience was reported by DeBrabander et al.<sup>17</sup> who described a 3-year-old boy who was treated with ethanol after a methanol ingestion, resulting in a peak measured blood methanol concentration of 290 mg/L. The ethanol infusion “was not well tolerated,” causing the emergence of irritability and aggressive behavior in the absence of hypoglycemia. The patient was switched to fomepizole and discharged uneventfully from the intensive care unit the next day.

## Conclusions

There is less published experience with fomepizole in the treatment of pediatric patients than there is for adults. The use of the older alcohol dehydrogenase inhibitor, ethanol, is similarly poorly documented in the pediatric population. The data described in this review, although anecdotal, suggest that fomepizole is efficacious in the pediatric population using the same dosage regimen as that used for adults.<sup>1–3</sup> Side effects appear to be unusual.

Finally, although the data reviewed here suggest that fomepizole is safe and effective in pediatric patients, and that in the majority of cases of ethylene glycol poisoning extracorporeal techniques are not necessary, the data may be skewed by publication bias if those patients with bad outcomes were not published. However, as publication bias generally favors the publication of adverse effects this factor, although incalculable, probably is not one of major significance.

## Declaration of interest

The author reports no declarations of interest. The authors alone are responsible for the content and writing of this paper.

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