Chapter A33: Fomepizole

Mary Ann Howland

INTRODUCTION

Fomepizole, a competitive inhibitor of alcohol dehydrogenase (ADH), prevents the formation of toxic metabolites from ethylene glycol and methanol. It also has a role in halting the disulfiram–ethanol reaction and in limiting the toxicity from a variety of xenobiotics that rely on ADH for metabolism to toxic metabolites. In addition, as both an inducer and an inhibitor of certain cytochrome P450 CYP enzymes, the presence of fomepizole leads to drug interactions.

HISTORY

In 1963, Theorell described the inhibiting effect of pyrazole on the horse ADH nicotinamide adenine dinucleotide (NAD\(^+\)) enzyme–coenzyme system.\(^{83,106}\) Pyrazole blocked ADH by complexation, and the administration of pyrazole to animals poisoned with methanol and ethylene glycol improved survival.\(^{107}\) However, pyrazole also inhibited other liver enzymes, including catalase and the microsomal ethanol-oxidizing system.\(^{75}\) Additional adverse effects of pyrazole administration resulted in bone marrow, liver, and kidney toxicity, and these effects increased in the presence of ethanol and methanol.\(^{87}\) These factors led to the search for less toxic compounds with comparable mechanisms of action.

In 1969, Li and Theorell found that both pyrazole and 4-methylpyrazole (fomepizole) inhibited ADH in human liver preparations,\(^ {74}\) and studies in rodents found that fomepizole, unlike pyrazole, was relatively nontoxic regardless of the presence or absence of ethanol.\(^ {14}\) Subsequent studies of fomepizole in monkeys and humans poisoned with methanol and ethylene glycol confirmed both the inhibitory effect and relative safety of fomepizole.\(^ {21,22,87}\)

PHARMACOLOGY
Chemistry

**Fomepizole** has a molecular weight of 82 Da, and a $pK_a$ of 2.91 at low concentrations and a $pK_a$ of 3.0 at high concentrations. The free base is used in the United States, whereas the salts are used in Europe. The free base is chemically equivalent to the chloride and sulfate salts at physiologic pH.²⁸

**Mechanism of Action**

**Fomepizole** is a potent competitive inhibitor of ADH with a very high affinity for ADH, thereby blocking the metabolism of methanol and ethylene glycol to their respective toxic metabolites.⁸⁸

Values for $K_m$ are estimated for the toxic alcohols and the $K_i$ with *fomepizole*. The smaller the $K_m$, the higher the affinity of the substrate (alcohol) for the enzyme, and the lower the concentration of the substrate to achieve $V_{\text{max}}$ (maximum velocity of the reaction of 50%) of the enzyme. The $K_i$ is the inhibition constant for the inhibitor. Studies in monkey and human liver tissue demonstrate that *fomepizole* is a competitive inhibitor of alcohol dehydrogenase.⁷⁸,⁹⁶ In monkey liver, *fomepizole* demonstrated very similar $K_i$'s for both ethanol and methanol at 7.5 and 9.1 μmol/L, respectively.⁷⁸ The affinity was 10 times higher when human liver was used.⁹⁵ Studies in monkeys demonstrate that a *fomepizole* concentration of 9 to 10 μmol/L (0.74–0.8 mcg/mL) is needed to inhibit the metabolism of methanol to formate.¹⁴,⁸⁷ In human liver, the concentration needed to achieve inhibition is about 0.9 to 1 μmol/L.⁷⁴,⁹⁵ The most recent trial using intravenous (IV) *fomepizole* attempted to maintain a serum *fomepizole* concentration above 10 μmol/L. Current dosing calls for a serum *fomepizole* concentration of 100 to 300 μmol/L to ensure a margin of safety.¹

Cytochrome P450 (CYP) 2E1 oxidizes ethanol and a number of other xenobiotics, including acetaminophen, carbon tetrachloride, nitrosamines, and benzene to toxic metabolites. *Fomepizole*, like ethanol and isoniazid, induces CYP2E1 in rat liver and kidney, but not in the lung, through a posttranscriptional mechanism via stabilization and not involving increase in messenger RNA.⁹⁰ However, when *fomepizole* is present, CYP2E1 is inhibited. It is not until after *fomepizole* is eliminated that the consequences of induction are manifest.¹⁸,¹¹²,¹¹³ In hepatocyte culture, *fomepizole* stabilizes and maintains the induced metabolic activity of the isoenzyme for about one week.¹¹⁴

**Pharmacokinetics**

The volume of distribution of *fomepizole* is about 0.6 to 1 L/kg; it is metabolized to 4-carboxypyrrozole, an inactive metabolite that accounts for 80% to 85% of the administered dose.⁸⁴,⁹⁰ In healthy human volunteers, oral doses of *fomepizole* are rapidly absorbed and demonstrate saturation and nonlinear kinetics.⁵⁵,⁸⁰,⁹⁰ The $K_m$ was estimated to be 75 μmol/L in 2 studies, and 0.94 μmol/L at a dose of 15 mg/kg to 2.49 μmol/L at a dose of 7 mg/kg in 2 analyses, although the reason for the discrepancy is not
First-order kinetics were exhibited at concentrations below the $K_m$, whereas zero-order elimination occurred at concentrations 100% to 200% of the $K_m$. Thus, elimination of fomepizole at doses of 10, 20, 50, and 100 mg/kg was 3.66, 5.05, 10.3, and 14.9 μmol/L/h, respectively. Classical Michaelis-Menten kinetics would predict that the elimination rate should be comparable at the 2 higher doses. The authors speculate that the differences are attributable to the existence of other metabolic pathways with different affinities that predominate at different fomepizole concentrations. Following multiple doses, the elimination of fomepizole increases at 36 to 48 hours, most likely because of autoinduction. After 96 hours fomepizole elimination apparently changed to first order elimination with a half-life of 1.5 to 2 hours, from zero order elimination. At a single dose of 20 mg/kg, the apparent half-life of fomepizole calculated from the linear portion of the curve was 5.2 hours and occurred when serum concentrations were less than 100 μmol/L. Peak concentrations after oral administration were achieved within 2 hours and were 132, 326, 759, and 1,425 μmol/L following 10, 20, 50, and 100 mg/kg doses, respectively. Every increase of 10 mg/kg in the oral dose of fomepizole raised the serum concentration 130 to 160 μmol/L. The renal clearance was low (0.016 mL/min/kg), and only 3% of the administered dose was excreted unchanged in the urine.

In the 2 pharmacokinetic studies in healthy volunteers, oral administration produced similar serum concentrations to IV fomepizole. The pharmacokinetics of IV fomepizole were studied in 14 patients being treated for ethylene glycol toxicity. A mean peak concentration of 342 μmol/L (200–400 μmol/L) was achieved following a loading dose of 15 mg/kg (183 μmol/kg). A significant weakness of this toxicokinetic study is that the effect of simultaneous serum ethanol concentrations was not analyzed. The lowest serum fomepizole concentration of 105 μmol/L was present at 8 hours after the loading dose. The rate of elimination was determined to be zero order at 16 μmol/L/h compared with a first-order elimination half-life of 3 hours during hemodialysis (HD). Other authors have reported similar fomepizole clearances (13 μmol/L/h).

A pharmacokinetic analysis in patients poisoned with methanol or ethylene glycol demonstrated a mean peak fomepizole concentration of 226 μmol/L (19 mcg/mL), an apparent half-life of 14.5 hours (in the presence of methanol or ethylene glycol), and an apparent half-life of 40 hours in the presence of ethanol, in addition to methanol or ethylene glycol. In the sole death, hepatic tissue contained 12 mcg/g of fomepizole, even when the serum concentration was less than 1 mcg/mL (12 μmol/L).

The hemodialysis clearance of fomepizole ranges from 50 to 137 mL/min. An analysis of the concentration of fomepizole in dialysis fluid revealed an extraction ratio of approximately 75% and a dialysance of 117 mL/min, which was very similar to a simultaneous ethylene glycol determination. The dialysance was similar to urea in a pig model and suggests no significant protein binding of fomepizole.

The pharmacokinetic interactions between fomepizole and ethanol were studied in a double-blind crossover design in healthy human volunteers. Fomepizole was given orally in doses of 10, 15, and 20 mg/kg 1 hour prior to oral ethanol at 0.5 to 0.7 g/kg as a 20% solution in orange juice. Fomepizole decreased the
elimination rate of ethanol by approximately 40%, from 12 to 16 mg/dL/h to about 7 to 9.5 mg/dL/h. When fomepizole was administered IV at 5 mg/kg over 30 minutes and ethanol was administered orally at doses to achieve a concentration of 50 to 150 mg/dL for 6 hours beginning at the end of the fomepizole infusion, the elimination of fomepizole was decreased by approximately 50%. This decrease occurred without a change in the amount or fraction of unchanged fomepizole appearing in the urine. The authors suggested that the ethanol probably inhibited the metabolism of fomepizole to 4-carboxypyrazole. A single low dose of fomepizole given to humans had a maximal effect on ethanol metabolism at 1.5 to 2 hours. Thus, ethanol and fomepizole mutually inhibit the elimination of the other, thereby maintaining higher serum concentrations than otherwise expected.

Methanol also decreases the elimination of fomepizole by approximately 25% in the monkey.

ROLE IN METHANOL TOXICITY

In Vitro and Animal Studies

Studies using human livers demonstrate the inhibitory effect of fomepizole on alcohol dehydrogenase. Studies in monkeys, the animal species that most closely resembles humans in metabolizing methanol, also demonstrate the inhibitory effect of fomepizole in preventing the accumulation of formate.

Human Experience

The 2 largest fomepizole case series to date involved 11 and 8 patients, respectively, who were given IV fomepizole in the approved US dosing regimen. Following administration, formate concentrations in all patients fell, and the arterial pH increased. Case reports demonstrate similar findings.

Effect on Methanol and Formate Concentrations

Methanol exhibits dose-dependent kinetics. At low doses (0.08 g/kg), which achieve serum concentrations of about 10 mg/dL, methanol elimination is first order, with a half-life of about 2.5 to 3 hours. In concentrations of approximately 100 to 200 mg/dL, methanol exhibits zero-order kinetics and is eliminated at about 8.5 to 9 mg/dL/h in untreated humans and 4.4 to 7 mg/dL/h in untreated monkeys. When monkeys were given 3 g/kg of methanol with resultant serum concentrations of about 500 mg/dL, the elimination of methanol exhibited apparent first-order kinetics. This alteration is likely caused by the greater contribution of other first-order pathways, such as pulmonary and urinary elimination, which account for a greater fraction of the total body clearance under these circumstances. Once fomepizole was administered, the elimination of methanol became first order in humans, and the half-life of methanol was about 54 hours but the range was from 22 to 87 hours. When the metabolism of methanol to formate is blocked, formate is eliminated with a half-life dependent on formate concentration, folate stores, kidney function, urinary pH, and exogenous folate and bicarbonate therapies. When formate was administered to monkeys in the absence
of methanol, formate half-life was 30 to 50 minutes. \(^{30}\) In monkeys given methanol followed by \textit{fomepizole}, the formate concentrations decreased by more than 80% in 2 hours. \(^{12}\) An analysis of formate concentrations in 6 patients with methanol poisoning treated with \textit{fomepizole}, folate, and \textit{sodium bicarbonate} revealed a formate half-life of \(235 \pm 83\) minutes. \(^{64}\) A more recent analysis involving 8 patients with methanol poisoning treated with \textit{fomepizole} and \textit{sodium bicarbonate} revealed a formate half-life of 156 minutes. \(^{49}\)

**ROLE IN ETHYLENE GLYCOL TOXICITY**

**In Vitro and Animal Studies**

Monkeys given 3 g/kg of ethylene glycol intraperitoneally recovered without treatment, whereas those given 4 g/kg died without therapy. All those given 4 g/kg of ethylene glycol with \textit{fomepizole} 50 mg/kg intraperitoneally survived. \(^{29}\)

**Human Experience**

The first 3 patients treated with oral \textit{fomepizole} improved clinically and tolerated the therapy. \(^{4}\) Subsequent case reports and case series using \textit{fomepizole} orally or IV, with or without hemodialysis, also demonstrated the effectiveness of \textit{fomepizole} in preventing glycolate accumulation. \(^{5,16,21,24,43,46,48,62,91,94,102}\)

**Effect on Ethylene Glycol and Glycolate Concentrations in Humans**

Kidney function is essential for the elimination of ethylene glycol. With normal kidney function, the half-life of ethylene glycol is about 8.6 hours. \(^{102}\) Based on pooled human data, the half-life of ethylene glycol after alcohol dehydrogenase is blocked by \textit{fomepizole} is about 14 to 17 hours in patients with normal kidney function, and about 49 hours in patients with impaired kidney function defined as a serum creatinine greater than 1.2 mg/dL. \(^{4,46,73,102}\) Based on a limited number of determinations, the renal clearance of ethylene glycol averaged 31.5 mL/min during the first 2 days; the corresponding creatinine clearance was 112 mL/min, and estimated total body clearance during \textit{fomepizole} therapy was 57 mL/min. \(^{5}\) These calculations suggest that the renal clearance of ethylene glycol accounted for only 55% of estimated total body clearance. In a study where neither kidney function was defined nor the amount of glycolate excreted unchanged by the kidneys described, glycolate had a mean half-life of \(10 \pm 8\) hours in patients treated with \textit{fomepizole} before hemodialysis, and a mean half-life of less than 3 hours during hemodialysis. \(^{57,65,91}\)

**ROLE IN TOXICITY FROM DIETHYLENE GLYCOL, DISULFIRAM, AND OTHER XENOBIOTICS**

\textit{Fomepizole} successfully terminated the adverse reactions resulting from the use of disulfiram administered to volunteers pretreated with a small dose of ethanol, in a chronic alcoholic surreptitiously given disulfiram
by his wife, and in 2 patients who intentionally ingested ethanol in addition to an overdose of disulfiram. \(^{76,99}\) Pretreatment with oral fomepizole was also successful in preventing the facial flushing and tachycardia typically associated with ethanol administration in ethanol-sensitive Japanese volunteers. \(^{53,54}\)

Several animal studies and a few case reports suggest that fomepizole is effective in limiting the toxicity secondary to diethylene glycol (DEG), triethylene glycol, and 1,3-difluoro-2-propanol. \(^{10,16,38,100,101,108}\) In particular an analysis of DEG concentrations and its metabolites in stored serum, urine and CSF from the Panama epidemic in 2006 revealed the presence of elevated 2-hydroxyethoxyacetic acid (HEAA) in serum and CSF and of diglycolic acid in serum, urine, and CSF in patients compared to controls. \(^{101}\) It is hypothesized that these metabolites are most likely responsible for the nephrotoxicity and neurotoxicity associated with DEG. \(^{31,66,67,97,101}\) Fomepizole blocks the metabolism of DEG to these toxic metabolites and is recommended as early as possible after ingestion before metabolism of DEG occurs \(^{10,88}\) along with urgent HD.

The role of fomepizole in overdoses secondary to 2-butoxyethanol (ethylene glycol monobutyl ether, butyl Cellosolve) is unclear, \(^{52}\) but fomepizole is reasonable for administration within several hours of ingestion and before rapid metabolism of butoxyethanol to butoxyacetic acid occurs. \(^{82,93}\) Isopropanol is metabolized in part by alcohol dehydrogenase, but fomepizole therapy is not indicated, as this intervention would prolong the metabolism of isopropanol to acetone without any clinical benefit. \(^{1,69}\)

**COMPARISON TO ETHANOL**

Ethanol effectively inhibits the metabolism of methanol and ethylene glycol to their respective toxic metabolites and has been used for many years. \(^{44,109,116}\) Although very inexpensive, ethanol has many disadvantages, compared to fomepizole. \(^{7,71,105,111}\) The affinity of ethanol for ADH is much lower than fomepizole, and rather than compete with the active site on ADH, it acts as a competitive substrate. \(^{88}\) Ethanol causes central nervous system depression that is at least additive to that of the methanol or ethylene glycol, and dosing difficulties occur as a result of the rapid and often unpredictable rate of ethanol metabolism (Antidotes in Depth: A34). \(^{7,9,111,115}\) Fomepizole has the advantage of being a very potent competitive inhibitor of alcohol dehydrogenase without producing CNS depression. Fomepizole dosing is much easier and does not require therapeutic monitoring of its serum concentration; administration and monitoring errors occur more frequently with ethanol. \(^{72,105}\) Limited adverse effects of fomepizole include local reactions at the site of infusion when concentrations exceeding 25 mg/mL are used, nausea, dizziness, anxiety, headache, rash, transiently elevated aminotransferases, and eosinophilia. Fomepizole is preferred to ethanol for all of the above reasons. Ethanol is recommended for use when fomepizole is not readily available with the exception that ethanol is most likely preferred in a mass casualty situation until sufficient supplies of fomepizole could be procured. \(^{72,103}\)

**ADVERSE EFFECTS AND SAFETY ISSUES**
Retinol dehydrogenase, an isoenzyme of ADH is responsible for converting retinol to retinal in the retina. For this reason, it was essential to study whether fomepizole would inhibit this enzyme and produce retinal damage. Studies in several animal species demonstrated that fomepizole has limited toxicity, with no ophthalmic toxicity. Two of the largest case series and 2 case reports confirm the lack of retinal toxicity with fomepizole and demonstrate the reversibility of methanol-induced visual toxicity when patients are treated with fomepizole and hemodialysis before permanent ophthalmic damage developed.

The LD₅₀ (median lethal dose for 50% of test subjects) of fomepizole in mice and rats is 3.8 mmol/kg after IV administration and 7.9 mmol/kg following oral administration. An oral placebo-controlled, double-blind, single-dose, randomized, sequential, ascending-dose study was performed in healthy volunteers to determine fomepizole tolerance at 10 to 100 mg/kg. There were no adverse effects in the 10- and 20-mg/kg groups, whereas at 50 mg/kg, 3 of 4 subjects experienced slight to moderate nausea and dizziness within 2.5 hours of fomepizole administration. All subjects reported these same symptoms at 100 mg/kg, which lasted for 30 hours in one individual without vital sign or laboratory abnormalities. The most common adverse effects of the use of fomepizole reported by the manufacturer (in a total of 78 patients and 63 volunteers) were headache (14%), nausea (11%), and dizziness, increased drowsiness, and dysgeusia or metallic taste (6%). Other less commonly observed adverse effects include phlebitis, rash, fever, and eosinophilia. A case report of a patient severely poisoned with ethylene glycol suggested a temporal association between IV fomepizole administration during hemodialysis and the development of bradycardia and hypotension. However, this patient was severely acidemic, and when the patient received the fomepizole postdialysis no such adverse effects were noted. Divided daily doses of fomepizole up to 20 mg/kg for 5 days were administered without any demonstrable toxicity. The most common laboratory abnormality after fomepizole administration is a transient elevation of aminotransferase concentrations, which was reported in 6 of 15 healthy volunteers. In the 2 largest case series of patients treated with fomepizole for toxic alcohol poisoning, there were no adverse events classified as “definitely” or “probably” related to fomepizole. One patient received fomepizole 99 times for repetitive ethylene glycol self-poisoning without adverse effects. Fomepizole safety and effectiveness in pediatric patients is not established, but children who have ingested ethylene glycol and methanol were treated successfully.

PREGNANCY AND LACTATION

Fomepizole is pregnancy category C. Animal studies have not been conducted. One case report of a pregnant woman treated twice with fomepizole for inhalation of a carburetor cleaner containing methanol is reported in the literature but follow-up information on the fetus was never obtained. The risks of methanol and ethylene glycol poisoning are so consequential (including neonatal death) that it is recommended that fomepizole be administered when toxicity is present or anticipated with these toxic alcohols. If fomepizole is not available, then ethanol is recommended. There are no studies that have examined the amount of fomepizole in breast milk although the low molecular weight suggests that it will be excreted into
breast milk. It is likely that the toxic alcohol for which the fomepizole is being used would also be excreted into breast milk. Therefore it is recommended that breast feeding be temporarily discontinued until fomepizole is predicted to be eliminated from the body (about 24 hours after the last dose) and the toxic alcohol has been eliminated.

**DOsing AND ADMINISTRATION**

The loading dose of fomepizole is 15 mg/kg IV, followed in 12 hours by 10 mg/kg every 12 hours for 4 doses. If therapy is necessary beyond 48 hours, the dose is then increased to 15 mg/kg every 12 hours, for as long as necessary. This increase is recommended because fomepizole stimulates its own metabolism. Patients undergoing hemodialysis require additional doses of fomepizole to replace the amount removed during hemodialysis.

The manufacturer recommends dosing fomepizole every 4 hours during hemodialysis. We recommend the administration of fomepizole at the beginning of hemodialysis if the last dose was given more than 6 hours earlier. At the completion of hemodialysis, we recommend the administration of the next scheduled dose if more than 3 hours have transpired, or one-half of the dose if 1 to 3 hours have passed. Following hemodialysis dosing of fomepizole every 12 hours is reinstituted.

It is expected that patients undergoing continuous renal replacement therapy (CRRT) such as continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF) would also require an increase in the dose of fomepizole. Theoretically since the amount of removal with these CRRT modalities is not as extensive as with HD, a reasonable recommendation would be to administer the fomepizole every 8 hours during the CVVHD or CVVHDF.

Fomepizole must be diluted in 100 mL of 0.9% sodium chloride solution or 5% dextrose in water (D5W) before IV administration, and then infused over 30 minutes to avoid venous irritation and thrombophlebitis. Once diluted, fomepizole remains stable for 24 hours when stored in a refrigerator or at room temperature.

Fomepizole therapy should be continued until the methanol or ethylene glycol is no longer present in sufficient concentrations to produce toxicity. We recommend continuing therapy until the serum toxic alcohol concentration is predicted or measured to be below 25 mg/dL in the absence of any acid–base disturbances.

The threshold concentrations for hemodialysis for methanol or ethylene glycol can be based on measurements when analyses can be done in a timely fashion. The duration of fomepizole therapy in the absence of hemodialysis can be estimated based on the assumption of half-life of the toxic alcohol when blocked with fomepizole. The half-life of methanol is approximately 54 hours in the presence of fomepizole with a range of 22 to 87 hours. The half-life of ethylene glycol in the presence of fomepizole is approximately 14 to 17 hours in patients with normal kidney function, and 49 hours in patients with impaired kidney function.
The need for hemodialysis is based on the presence of toxic metabolites inferred by the presence of metabolic acidosis and end-organ damage; the ability of the kidney to eliminate ethylene glycol, glycolic acid and formate, the risk benefit of hemodialysis, and the length of time to remain hospitalized for elimination of the remaining methanol and ethylene glycol.\textsuperscript{50,98}

**FORMULATION AND ACQUISITION**

Fomepizole is marketed in branded and generic formulations in 1.5-mL vials of 1 g/mL. Temperatures of less than 77°F (25°C) cause the contents of the fomepizole vials to solidify. Warming reliquifies the product without adversely affecting its potency.

**SUMMARY**

Fomepizole is a potent competitive inhibitor of ADH that inhibits the metabolism of methanol, ethylene glycol, diethylene glycol and other xenobiotics that use ADH in the formation of toxic metabolites.

Once ADH is blocked and sustained, the decision to use hemodialysis depends on how much damage has occurred to the organs of elimination, the acid-base status of the patient, and how well the body can eliminate both the parent compound and the toxic metabolites formed prior to fomepizole administration.

Fomepizole is safe and, although it has been used successfully orally, only an IV dosing regimen is approved and available.

Fomepizole is more costly than ethanol, but its many advantages over ethanol, including the ability to deliver care outside an intensive care unit, which makes fomepizole the preferred antidote in most circumstances.

Ethanol is likely to be preferred in a mass casualty situation until sufficient supplies of fomepizole are procured.

**REFERENCES**


