ANTIDOTES IN DEPTH

Fomepizole

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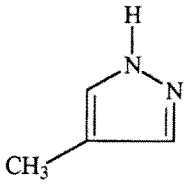

Fomepizole is a competitive inhibitor of alcohol dehydrogenase (ADH) that prevents the formation of toxic metabolites from ethylene glycol and methanol. It may also have a role in halting the disulfiram–ethanol reaction, and in limiting the toxicity from a variety of xenobiotics that rely on alcohol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

HISTORY

In 1963, Theorell and associates described the inhibiting effect of pyrazole on the horse ADH-NAD^+ (nicotinamide adenine dinucleotide) enzyme–coenzyme system.[71] They noted that pyrazole appeared to block ADH by complexation, and that the administration of pyrazole to animals poisoned with methanol and ethylene glycol improved survival.[72] However, pyrazole also inhibited other liver enzymes, including catalase and the microsomal ethanol-oxidizing system.[50] Additional adverse effects of pyrazole administration resulted in bone marrow, liver, and renal toxicity, and these effects increased in the presence of ethanol and methanol.[61] 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.[49] Studies in rodents found that fomepizole was relatively nontoxic regardless of the presence or absence of ethanol.[10] Subsequent studies of fomepizole in monkeys and humans poisoned with methanol and ethylene glycol demonstrated both the inhibitory effect and relative safety of fomepizole.[15,16,61]

PHARMACOLOGY

Fomepizole has a molecular weight of 82 daltons and a pKa of 2.91 at low concentrations and a pKa of 3.0 at high concentrations. The freebase is used in the United States, whereas the salts are used in Europe. The freebase is chemically equivalent to the chloride and sulfate salts at physiologic pH.[20]

Values for K_m (Michaelis-Menten dissociation constant) have been estimated for the toxic alcohols, along with the value for K_i (dissociation of enzyme-inhibitor complex inhibition constant) 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 that is needed to half saturate the enzyme. Studies in monkey and human livers demonstrate that fomepizole is a competitive inhibitor of alcohol dehydrogenase.[53,68] In monkey liver, fomepizole demonstrated very similar K_is for both ethanol and methanol at 7.5 and 9.1 μmol, respectively.[53] In this same model, the K_m was 3.2 for ethanol and 20.1 μmol for methanol, demonstrating a 6 times higher affinity of ethanol for alcohol dehydrogenase than methanol.[53] The affinity was 15 times higher when human liver was used.[67] Studies in monkeys demonstrate that a fomepizole concentration of 9–10 μmol/L (0.74–0.8 μg/mL) is needed to inhibit the metabolism of methanol to formate.[10,61] In human liver, the level needed to achieve inhibition is about 0.9–1 μmol/L.[49,67] The most recent trial that used intravenous fomepizole attempted to maintain a serum fomepizole concentration above 10 μmol/L. Current dosing calls for a serum fomepizole concentration of 100–300 μmol/L to insure a margin of safety.[1]

The CYP2E1 isozyme oxidizes ethanol and a number of other xenobiotics to toxic metabolites, including acetaminophen, carbon tetrachloride, nitrosamines, and benzene. Fomepizole, like ethanol and isoniazid, has dual effects on this isozyme. Fomepizole induces this isozyme in rat liver and kidney, but not in the lung, through a posttranscriptional mechanism not involving increased mRNA. However, when fomepizole is present, the isoenzyme is inhibited. It is not until after fomepizole is eliminated, that the consequences of induction are manifest.[13,76,77] In hepatocyte culture, fomepizole stabilizes and maintains the induced metabolic activity of the isoenzyme for about 1 week.[78]

PHARMACOKINETICS

The volume of distribution of fomepizole is about 0.6–1 L/kg; it is metabolized to 4-carboxpyrazole, an inactive metabolite that accounts for 80–85% of the administered dose.[58] In healthy human volunteers, oral doses of fomepizole were rapidly absorbed and demonstrated saturation and nonlinear kinetics.[37] The K_m (concentration at which the maximum elimination rate is 50%) was estimated to be 75 μmol/L.[37,56] First-order kinetics were exhibited at concentrations below the K_m, whereas zero-order elimination occurred at concentrations 100–200% of the K_m.[37] Thus elimination of fomepizole at doses of 10 mg/kg, 20 mg/kg, 50 mg/kg, and 100 mg/kg was 3.66, 5.05, 10.3, and 14.9 μmol/L/h, respectively.[37] Classical Michaelis-Menten kinetics would predict that the elimination rate should be the same at the two higher doses, but this is not the case. The authors speculate that multiple metabolic pathways with different affinities exist and predominate at different fomepizole concentrations. At a dose of 20 mg/kg, the 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 1425 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

130–160 μmol/L.[37] The renal clearance was low (0.016 mL/min/kg), and only 3% of the administered dose was excreted unchanged in the urine.[37]

In a pharmacokinetic study in healthy volunteers, oral administration produced similar serum concentrations to IV fomepizole.[55] The pharmacokinetics of intravenous fomepizole were studied in 14 patients being treated for ethylene glycol toxicity.[45] 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).[58,69] A significant weakness of the study affecting toxicokinetic data is that the effect of simultaneous plasma ethanol concentrations was not analyzed. The lowest fomepizole plasma 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 as compared with a first-order elimination half-life of 3 hours during hemodialysis. Other authors have reported similar fomepizole clearances (12.99 μmol/L/h).[17] A recent pharmacokinetic analysis in patients poisoned with methanol or ethylene glycol demonstrated a mean peak fomepizole concentration of 19 μg/mL (226 μmol/L), an apparent half-life of 14.5 hours (in presence of methanol or ethylene glycol), and an apparent half-life of 40 hours in the presence of ethanol along with methanol or ethylene glycol. In the sole death, hepatic tissue contained 12 μg/g of fomepizole, even when the plasma concentration was <1 μg/mL (12 μmol/L).[75]

The plasma clearance of fomepizole during hemodialysis was 230 mL/min. Previous analysis using determinations of 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.[26] The dialysance of fomepizole was similar to urea in a pig model and suggests no significant protein binding of fomepizole.[38]

The pharmacokinetic interactions between fomepizole and ethanol were studied in a double-blind crossover design in healthy human volunteers.[42] Fomepizole was given orally in doses of 10, 15, and 20 mg/kg 1 hour prior to oral ethanol at 0.5–0.7 g/kg as a 20% solution in orange juice. Fomepizole decreased the elimination rate of ethanol by approximately 40%, from 12–16 mg/dL/h to about 7–9.5 mg/dL/h. When intravenous fomepizole was administered at 5 mg/kg over 30 minutes and ethanol was administered orally at doses to achieve a concentration of 50–150 mg/dL for 6 hours beginning at the end of the fomepizole infusion, the elimination of fomepizole was decreased by approximately 50%.[42] 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 by the cytochrome P450 system. A single low dose of fomepizole given to humans had a maximal effect on ethanol metabolism at 1.5–2 hours.[9] Thus ethanol and fomepizole mutually inhibit the elimination of each other, prolonging their respective plasma concentrations. Methanol also decreases the elimination of fomepizole by approximately 25% in the monkey.[61]

METHANOL

In Vitro and Animal Studies

Studies using human livers demonstrate the inhibitory effect of fomepizole on alcohol dehydrogenase.[67] Studies in monkeys, the animal species that most closely resembles humans in metabolizing methanol, also clearly demonstrate the inhibitory effect of fomepizole in preventing the accumulation of formate.[8,61,62]

Human Experience

The largest fomepizole case series to date involved 11 patients who were given IV fomepizole in the approved US dosing regimen.[16] Following administration, formate concentrations in all patients fell and the arterial pH increased.[16] Case reports demonstrate similar findings.[17,28,32]

Effect of Fomepizole on Methanol and Formate Concentrations

Methanol exhibits dose-dependent kinetics.[41] 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 2.5–3 hours.[45,48] In concentrations of about 100–200 mg/dL, methanol exhibits zero-order kinetics and is eliminated at about 8.5–9 mg/dL/h in untreated humans[41] and 4.4–7 mg/dL/h in untreated monkeys.[24,64] 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 may account for a greater fraction of the total body clearance under these circumstances.[41] Once fomepizole is administered, the elimination of methanol becomes first order in humans, and the half-life of methanol is about 54 hours.[16] When the metabolism of methanol to formate by alcohol dehydrogenase is blocked, formate is eliminated with a half-life dependent on dose and the uncertain effect of folate and bicarbonate therapies. When formate was administered to monkeys in the absence of methanol, formate half-life was 30–50 minutes.[21] In monkeys given methanol followed by fomepizole, the formate levels decreased by more than 80% in 2 hours.[8] A recent analysis of formate concentrations in 6 patients with methanol poisoning treated with fomepizole, folate, and sodium bicarbonate revealed a formate half-life of 235 ± 83 minutes.[46]

ETHYLENE GLYCOL

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 fomepizole survived.[21]

Human Experience

The first 3 patients treated with oral fomepizole improved clinically and tolerated the therapy.[4] Subsequent case reports and case series using fomepizole orally or IV, with or without hemodialysis, have also demonstrated effectiveness of fomepizole in preventing glycolate accumulation.[5,11,15,31,34,44,63,69]

Effect of Fomepizole on Ethylene Glycol and Glycolate Concentrations in Humans

Renal function is essential in the elimination of ethylene glycol. With normal renal function, the half-life of ethylene glycol is about 8.6 hours.[69] Based on pooled human data, the half-life of ethylene glycol after alcohol dehydrogenase is blocked by fomepizole is about 14–17 hours in those patients with normal renal function, and about 49 hours in patients with impaired renal function.[4,31,69] 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 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 renal function was defined nor the amount of glycolate (MW = 76 daltons) excreted unchanged by the kidneys described, glycolate had a mean half-life of 10 ± 8 hours in patients treated with fomepizole before hemodialysis, and a mean half-life of less than 3 hours during hemodialysis.[63]

SAFETY AND ADVERSE EFFECTS

Retinol dehydrogenase, which is responsible for converting retinol to retinal in the eye, is an isozyme of ADH. As such, it was essential to study whether fomepizole would inhibit this enzyme and subsequently produce retinal damage.[61] Studies in several animal species demonstrate that fomepizole is relatively nontoxic, with no demonstrable signs of ophthalmic toxicity.[8] Two of the largest case series, and 2 recent 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 toxicity developed.[15,16,25,70]

The LD_{50} (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.[52] An oral placebo-controlled, double-blind, single-dose, randomized, sequential, ascending-dose study was performed in healthy volunteers to determine fomepizole tolerance at 10–100 mg/kg.[41] 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 comparable symptoms at 100 mg/kg, which lasted for 30 hours in 1 individual without vital sign or laboratory abnormalities noted. The most common adverse effects of the use of fomepizole reported by the manufacturer (in a total of 76 patients and 63 volunteers) were headache 12%, nausea 11%, and dizziness 7%. Other less commonly observed adverse effects include phlebitis, rash, fever, and eosinophilia. Similarly, divided daily doses of fomepizole up to 20 mg/kg for 5 days have been administered without any demonstrable toxicity.[60] The most common laboratory abnormality after fomepizole administration is a transient elevation of aminotransferase levels, which was reported in 6 of 15 healthy volunteers.[40] 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.[15,16] Fomepizole is not approved for use in children, but has been used successfully in children who have ingested ethylene glycol and methanol.[6,12,18,22,23,33,75]

Fomepizole is pregnancy category C and thus should be utilized appropriately as indicated.

DISULFIRAM AND OTHER XENOBIOTICS

Fomepizole successfully terminated the adverse reactions resulting from the use of disulfiram administered to volunteers pretreated with a small dose of ethanol and those reactions occurring in a chronic alcoholic surreptitiously given disulfiram by his wife.[51] Pretreatment with oral fomepizole was also successful in preventing the facial flushing and tachycardia typically associated with ethanol administration in ethanol-sensitive Japanese subjects.[35,36]

Limited animal studies and a few case reports suggest that fomepizole may be effective in limiting the toxicity secondary to diethylene glycol, triethylene glycol and 1,3-difluoro-2-propanol.[11,27,73] The role of fomepizole in overdoses secondary to 2-butoxyethanol (ethylene glycol monobutyl ether, butyl cellosolve) is unclear, but fomepizole may be useful if administered within several hours of ingestion and before rapid metabolism of butoxyethanol to butoxyacetic acid occurs.[57] Isopropanol is probably metabolized at least in part by alcohol dehydrogenase, but fomepizole therapy is not indicated, as this intervention would prolong the metabolism of isopropanol to acetone.[1]

COMPARISON TO ETHANOL

Ethanol has been used for many years to inhibit the metabolism of methanol and ethylene glycol to their respective toxic metabolites. Although very inexpensive, ethanol has many disadvantages, compared to fomepizole. Ethanol causes central nervous system depression that is at least additive to that of the methanol or ethylene glycol; dosing difficulties occur as a result of the rapid and often unpredictable rate of ethanol metabolism, and prolonged ethanol administration causes tolerance to ethanol to develop; an intravenous formulation of ethanol is not readily available; the serum concentrations of ethanol must be closely monitored; a 5 or 10% intravenous preparation of ethanol is hyperosmolar;[79] and there is a great potential for hyponatremia and hypoglycemia or other ethanol-related adverse effects, such as pancreatitis and hepatitis. In contrast to all of these problems associated with ethanol administration, fomepizole has the advantage of being a very potent inhibitor of alcohol dehydrogenase without producing central nervous system (CNS) depression. Fomepizole dosing is much easier without a need for serum concentration monitoring, thus allowing for every-12-hour dosing except during hemodialysis, when dosing should occur every 4 hours. Limited adverse effects of fomepizole include local reactions at the site of infusion when concentrations exceeding 25 mg/mL are employed, nausea, dizziness, anxiety, headache, rash, transiently elevated aminotransferases, and eosinophilia.

Fomepizole is preferred to ethanol for all of the above reasons. Ethanol should only be used when fomepizole is not readily available. Hospitals should be encouraged to stock fomepizole.

DOSING

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. Fomepizole should be administered at the beginning of hemodialysis if the last dose was more than 6 hours earlier. At the completion of hemodialysis, administer the next scheduled dose if more than 3 hours has transpired on one-half of the dose if 1–3 hours has passed.

The fomepizole dose must be diluted in 100 mL of 0.9% sodium chloride solution or D_5W (dextrose 5% in water) prior to IV administration, and then infused over 30 minutes to avoid venous irritation

and phlebosclerosis. Once diluted, fomepizole remains stable for 24 hours when stored in the refrigerator or at room temperature.[1]

Fomepizole therapy should be continued until the methanol or ethylene glycol is no longer present in sufficient concentrations to produce toxicity. Although these concentrations are not precisely known, 25–50 mg/dL of either ethylene glycol or methanol is a conservative estimate that can be lowered in the presence of acid–base disturbances.[1–3]

The threshold concentrations for hemodialysis of 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.[11] The half-life of ethylene glycol in the presence of fomepizole is approximately 14–17 hours in patients with normal renal function, and 49 hours in patients with impaired renal function.[4,34,69]

AVAILABILITY

Fomepizole is marketed as Antizol injection by Orphan Medical in a tray pack containing 4 vials (1.5 mL vials of 1 g/mL). Temperatures of <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 alcohol dehydrogenase that is useful in inhibiting the metabolism of methanol, ethylene glycol, and other xenobiotics that use alcohol dehydrogenase in the formation of toxic metabolites. Once alcohol dehydrogenase is blocked, the decision to use hemodialysis depends on how much damage has occurred to the organs of elimination, and how well the body can eliminate both the parent compound and the toxic metabolites formed prior to fomepizole administration. Fomepizole appears to be safe and, although it has been used successfully orally, only an intravenous dosing regimen is approved and available. Although the price of fomepizole is higher than ethanol, its many advantages over ethanol, including the ability to often deliver care ouside the ICU, make fomepizole the preferable antidote. Hospitals should be encouraged to stock fomepizole.

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