PHARM PROFILE

FOMEPIZOLE

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Fomepizole, a synthetic alcohol dehydrogenase inhibitor used as an antidote for ethylene glycol (EG) poisoning in dogs, represents a significant therapeutic advantage over the use of the traditional EG antidote, ethanol.¹ ²

PHARMACOLOGY AND PHARMACOKINETICS

Fomepizole (4-methylpyrazole) acts as a competitive inhibitor of alcohol dehydrogenase, a liver enzyme.³ EG is oxidized to glycoaldehyde by alcohol dehydrogenase, resulting in toxic metabolites (glycolic, glyoxalic, and oxalic acid) that are responsible for metabolic acidosis and renal tubule damage in poisoned dogs. Following inhibition of alcohol dehydrogenase by fomepizole, unchanged EG and its metabolites are excreted in the urine and renal damage is avoided.

The effectiveness of fomepizole depends on the timing of administration; it must be injected into the bloodstream before ingested EG has been completely metabolized. If laboratory testing reveals any EG remaining in the bloodstream after ingestion, treatment with fomepizole is warranted to prevent further damage.⁴

Cats do not respond to dosages of fomepizole that are effective in treating dogs with EG poisoning.⁵ This is thought to be because alcohol dehydrogenase has lower enzymatic activity in the feline liver than in the canine liver.¹ Consequently, ethanol is considered the treatment of choice in cats.⁵ However, it has been suggested that higher doses of fomepizole may be beneficial in EG-poisoned cats, and studies are being conducted to support its use in this species.⁶

Fomepizole is excreted primarily by the kidneys and exhibits a dose-dependent accumulation over time, causing a need for reduction in subsequent doses.⁷ In a study evaluating the toxicity of fomepizole when administered intravenously to dogs twice daily for 14 days,⁸ it was determined that dogs receiving the drug at 20 mg/kg or less did not suffer from cumulative effects.

INDICATIONS

Fomepizole is labeled for the treatment of EG toxicosis in dogs. Several authors have determined that fomepizole is more effective than ethanol in the treatment of EG toxicity in dogs.⁹-¹¹ Based on these results, Dial and colleagues⁷,¹² examined the effect of time after EG ingestion on efficacy of fomepizole and concluded that fomepizole is effective even if treatment is delayed for 5 to 8 hours after EG ingestion as long as the dog is not azotemic and EG has not been completely metabolized.

CAUTIONS

Contraindications

There are no known contraindications to the use of fomepizole.⁸ However, the drug can produce central nervous system (CNS) depression at higher doses (more than 20 mg/kg), and monitoring is necessary when other medications that depress the CNS are administered concomitantly.⁸

Precautions

Fomepizole must be diluted (1:20) with 0.9% sodium chloride before intravenous administration. Rapid infusion may produce irritation of the vein or phlebosclerosis.⁹ Competitive substrates (e.g., ethanol) should not be given with fomepizole because they potentiate CNS and respiratory depression.

Adverse Reactions

Dose-related CNS depression can occur at doses higher than 20 mg/kg or if fomepizole accumulates after successive doses. Anaphylaxis after fomepizole administration was reported in a dog receiving the drug as part of an experimental study.⁵

ACUTE TOXICITY

Administration of fomepizole at 25 mg/kg twice daily for 14 days has re-
sulted in weight loss and anorexia. Doses of 50 mg/kg and higher have resulted in ataxia; tremors; hypothermia; elevated liver chemistries; and increased blood urea nitrogen and creatinine levels, erythrocytes, hemoglobin, and hematocrit.13

**DOSAGE AND ADMINISTRATION**

As soon as possible after poisoning with EG, fomepizole should be administered intravenously at a dose of 20 mg/kg. Twelve, 24, and 36 hours after administration of the loading dose, intravenous doses of 15, 15, and 5 mg/kg, respectively, should be given. If signs have not improved after 36 hours or if remaining EG is suspected in the bloodstream, treatment with 5 mg/kg of fomepizole should be continued every 12 hours until signs improve.13

Additional therapy, such as fluid and electrolyte replacement, may be warranted. If there is a confirmation of EG ingestion, emesis should be induced, followed by administration of activated charcoal by mouth within 1 to 2 hours of ingestion.8

**PREPARATIONS**

Antizol-Vet® (Orphan Medical, Inc., Minnetonka, MN) is distributed as a kit consisting of a 30-ml vial of 0.9% sodium chloride and a 1.5-ml vial of fomepizole that is available to veterinarians for $240 each. In the event that the fomepizole solution has solidified, either holding the vial firmly in the hand or running warm water over it will result in reliquefaction. Stability (24-month shelf life), efficacy, and safety are not affected by solidification. The contents in the 1.5-ml fomepizole vial should be injected into the sodium chloride vial and mixed thoroughly. The reconstituted vial should be used within 72 hours and should be stored at room temperature (15°C to 30°C).13

Due to the availability of the Antizol-Vet® kit, compounding is generally not necessary. However, a compounding procedure for intravenous injection is available through the Professional Compounding Centers of America. The final concentration of the compounded fomepizole is 50 mg/ml and is stable for 6 months.

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**REFERENCES**