

TOXALERT

June 2004
Volume 21 Issue 1



Fomepizole (Antizol®)

Frequently Asked Questions

SUZANNE DOYON, MD, ACMT
MEDICAL DIRECTOR
MARYLAND POISON CENTER

Fomepizole received FDA approval in 1997 and is now marketed as Antizol® injection by Orphan Medical. It is indicated in the treatment of poisonings with methanol and ethylene glycol.

Fomepizole is a competitive inhibitor of alcohol dehydrogenase. It works to keep both methanol and ethylene glycol in their (relatively non-toxic) parent form. The loading dose of fomepizole is 15 mg/kg IV followed in 12 hours by 10 mg/kg IV every 12 hours for 4 doses and then increased to 15 mg/kg IV every 12 hours as necessary. The increase in maintenance dose from 10 to 15 mg/kg is recommended because fomepizole autoinduces its own metabolism. Patients undergoing hemodialysis require dose adjustments because of the amount of fomepizole that will be removed during dialysis. The dose can be diluted in 100 mL of normal saline or D5W and then infused IV over 30 minutes.

A recent survey by Maryland Poison Center found that fomepizole is available in 90% of hospitals within our area.

FAQs

Which is worse; ethylene glycol or methanol poisoning?

Both types of poisonings are very serious, but methanol poisonings have a higher mortality rate. Methanol is a component of windshield washer fluid and is toxic in doses of 0.1 mL/kg of 100% solution. It is associated with a delay in onset of symptoms. Severe anion gap metabolic acidosis and visual disturbances are likely. Case fatality ratio is higher than with ethylene glycol.

Ethylene glycol is a component of radiator fluid and antifreeze and is toxic at doses of 0.2 mL/kg of 100% solution. Onset of symptoms is more rapid. Early effects are CNS depression and severe anion gap metabolic acidosis. Later effects are

Fomepizole is a safe and effective antidote for methanol and ethylene glycol poisonings.

It is easier than ethanol to dose and administer, and has fewer adverse effects.

Fomepizole FAQ's

cardiopulmonary and acute renal failure. Although exposures to ethylene glycol are more frequent than methanol, ethylene glycol has a lower case fatality ratio.

I gave the loading dose of fomepizole to the patient...now what?

Initial steps include providing supportive care and intubation and ventilation as needed.

The Maryland Poison Center also recommends the following:

- Correction of the pH with administration of sodium bicarbonate as needed.
- Correction of symptomatic hypocalcemia with administration of calcium chloride as needed.
- Administration of cofactors especially if acidosis is present. For ethylene glycol poisoning the cofactors are thiamine 100 mg IV qd and pyridoxine 100 mg IV qd. For methanol poisoning the cofactor is folate 1 mg/kg (max 50 mg) IV q4h.
- Consultation with Nephrology. Emergency hemodialysis might be needed if serum levels of methanol or ethylene glycol are extremely high, if there is evidence of renal insufficiency with ethylene glycol poisoning, or if intractable or life-threatening metabolic acidosis is present.

My patient is receiving fomepizole and is completely asymptomatic...can I send him to psychiatry?

No! Looks can be deceptive. Fomepizole should be administered IV q12 hours until ethylene glycol and methanol levels are below 20 mg/dL and the metabolic acidosis has resolved. Careful monitoring of mental status, acid base status and renal function is recommended during fomepizole therapy. Fomepizole-treated patients, especially the early presenters, appear completely well. Premature transfer to psychiatry is not recommended.

Can I give fomepizole and ethanol together for enhanced effect?

Enzyme inhibition is 98% complete with fomepizole. The additional enzyme inhibition offered by the concomitant administration of ethanol is negligible. Adverse effects of ethanol infusion are frequent and significant. Bottom line, there is no reason to give both medications concomitantly.

What if I am wrong and I administer fomepizole to a patient needlessly?

The treatment of ethylene glycol and methanol poisonings often requires the empiric administration of fomepizole to patients with a history of ingestion or unexplained anion gap metabolic acidosis (i.e. before the diagnosis of ethylene glycol or methanol poisoning is confirmed by the laboratory). Stat serum levels have a 6-12 hour turnaround time.

The good news is that fomepizole is extremely safe. Administration of fomepizole to healthy human volunteers is associated with dizziness, occasional mild, transient and clinically insignificant elevation of hepatic transaminases and rarely, transient eosinophilia. It is a safe antidote and physicians should not hesitate to prescribe fomepizole to a patient with suspected ethylene glycol or methanol poisoning.

Are there other poisonings where fomepizole administration would be useful?

Physicians have administered fomepizole to patients with isopropanol and diethylene glycol poisonings. In the case of isopropanol (rubbing alcohol) poisoning, administration of fomepizole will delay metabolism and prolong the toxicity of the drug by maintaining it in its highly toxic parent form. It is best to refrain from administering fomepizole and let the alcohol dehydrogenase enzyme metabolize the isopropanol to acetone and water as fast as possible.

Fomepizole FAQ's

In the case of diethylene glycol (e.g. component of brake fluid, fog juice) poisoning, administration of fomepizole is supported by some authors. Diethylene glycol is 60% excreted unchanged in the urine. A small amount of diethylene glycol is converted to a nephrotoxic metabolite (HEAA) and an even smaller amount is converted to ethylene glycol. In one case report, fomepizole administration to a diethylene glycol-poisoned patient yielded a dramatic response. There is concern, however, that administration of fomepizole to diethylene glycol-poisoned patients only shifts metabolism away from the formation of some nephrotoxic metabolites (glycolic acids) toward the formation of other, potentially worse, nephrotoxic metabolites (HEAA).

I heard fomepizole is costly, is that true?

Yes, fomepizole is expensive. For a normal size adult, each dose will average \$1000. However, fomepizole can also be a cost saving antidote.

Fomepizole has dramatically changed the disposition of patients poisoned with ethylene glycol and methanol. Non-academic fomepizole-treated patients, pediatric or adult, no longer require an ICU bed. Some ethylene glycol-poisoned patients can be treated with fomepizole alone and will not require

hemodialysis. Sparing patients (and hospitals) costly ICU beds and averting the costs and potential complications of hemodialysis treatment is reason enough to use fomepizole.

But there are even more reasons to use fomepizole. Frequent serum levels of fomepizole are not necessary (unlike ethanol). Fomepizole does not require frequent neurological checks or monitoring for hypoglycemia (unlike ethanol). This translates into less laboratory expense and less hands-on nursing or technician time. Overall the cost savings are important.

I have used ethanol infusions for years; why switch?

	Fomepizole	Ethanol
Easy to dose	yes	no
Easy to administer	yes	no
Favorable adverse effect profile	yes	no
FDA approved for ethylene glycol and methanol poisonings	yes	no
Saves ICU beds	yes	no
Averts hemodialysis	maybe	no
Inexpensive	no	yes
Available	yes	yes

Coming Soon: Maryland Poison Center's 2003 Annual Report

Here are the highlights:

- In 2003, the Maryland Poison Center (MPC) received over 60,000 calls.
- MPC staff safely managed 75% of all poisoning cases at home or at the site of the poisoning.
- 33% of cases had no effect, and 59% reported only minor effects from the exposure.
- There were 24 poisonings reported to the Maryland Poison Center that resulted in death.
- Over 17,000 Marylanders received poison prevention education materials from the MPC.
- More than 900 health professionals attended programs given by MPC staff in 2003.

To request a copy of our annual report, call 410-706-7604 or email lbooze@rx.umaryland.edu



20 North Pine Street
Baltimore, MD 21201

1-800-222-1222

Pre-sorted Standard
U.S. Postage
PAID
Permit No. 6735
Baltimore, MD



TOXNOTES

My patient is complaining of chest pain and headache after using an ephedra-free dietary supplement for a few days. Could her symptoms be related to the supplement?

Yes, ephedra-free dietary supplements often contain other stimulants and herbal ingredients that can result in significant cardiovascular effects. An FDA ban on the sale of dietary supplements containing ephedra (ma huang) went into effect April 12, 2004 as a result of hundreds of patients experiencing serious adverse events including heart attack and stroke. Many supplements are now labeled "ephedra-free" but contain other stimulant herbals and drugs such as caffeine, guarana (providing 3-5% caffeine), bitter orange (citrus aurantium), synephrine, calamus extract and sida cordifolia. In some cases, cardiovascular responses have been shown to occur after a single dose. Further complicating the situation, some products labeled as "ephedra-free", "legal speed", "herbal ecstasy" and "street drug alternative" have been found to contain unlabeled ingredients such as ephedra, diphenhydramine, dextromethorphan, gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL).

TOXALERT

Institute of Medicine Report on Poison Centers

The Institute of Medicine has published a report on the future of poison prevention and control services in the United States. They examined the role of poison control services within the context of the public health system to provide a systematic approach to long-term support for these services. Recommendations of the IOM address:

1. essential functions of poison centers;
2. integrating poison centers with public health agencies;
3. cost, quality and staffing of poison centers;
4. federal funding of poison centers;
5. certification of poison centers;
6. poisoning data collection and surveillance.

The entire IOM report can be found at
<http://www.nap.edu/books/0309091942/html/>