



VET TALK

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American College of Veterinary Pharmacists

'Tis the Season for Antifreeze...and its Toxicities!

Introduction

Antifreeze is known to most as the neon green liquid that goes into our cars to lower the freezing point and prevent our radiators from locking up in cold weather. However, to veterinarians and veterinary pharmacists, it is ethylene glycol, a source of tens of thousands of animal poisonings each year, the majority of which occur in late fall, winter, and early spring which is why the timing appeared suitable for this newsletter. The other reason for publishing this article now is that the antidote for antifreeze poisoning, Antizol-Vet® (fomepizole), is on indefinite backorder. However, before there was an official antidote, there was compounded fomepizole (4-methylpyrazole) and ethanol as solutions for this common toxicity most often seen in our pet dogs, though occasionally noted in cats.

Pathophysiology/Etiology of Ethylene Glycol (EG) Toxicity

This chemical is water-soluble and is rapidly and completely absorbed and distributed within the body. In dogs, peak blood concentrations occur within 3 hours of ingestion. Although the parent compound EG, C₂H₆O₂, may cause some alteration of mental status, it is a relatively nontoxic compound before it is metabolized for it is the metabolites which cause the distinct toxicity associated with this compound. In order to understand how EG becomes toxic, one must first examine the ethanol metabolic pathway. Ethanol is metabolized by the alcohol dehydrogenase (ADH) enzyme pathway located in the liver and gastric mucosa, and by the cytochrome P-450 (CYP) mixed function oxidase system in the liver. The CYP-450's are subject to greater inducibility than alcohol dehydrogenase which can alter patient specific

outcomes. As with ethanol and methanol, EG is also metabolized by ADH to form glycoaldehyde which is then oxidized to glycolate, glyoxalate, and oxalate. Glycolate and oxalate are responsible for metabolic acidosis and renal damage. This is because ethylene glycol metabolites target the kidney and lead to oliguric or anuric acute renal injury, which in turn slows elimination of ethylene glycol making toxicity worst. The process of renal failure is primarily due to glycolate-induced direct damage to tubules, although tubule obstruction from precipitated oxalate crystals may contribute as well. Hypocalcemia in ethylene glycol overdose results from calcium oxalate formation. When EG is ingested, a profound anion gap metabolic acidosis develops, which directly correlates with the accumulation of toxic acid metabolites.



Clinical Signs and Symptoms of an Overdose

Clinical signs are dose- and time-dependent and can be divided into those caused by un-metabolized ethylene glycol and those caused by its toxic metabolites representing the 3 phases of overdose.

Phase I: Acute onset (30min-12 hours) of clinical signs is almost immediate and

resembles ethanol (alcohol) intoxication. Dogs and cats exhibit vomiting due to GI irritation, polydipsia, polyuria, and neurologic signs such as CNS depression, stupor, ataxia, knuckling, decreased withdrawal or righting reflexes. Polydipsia occurs due to osmotic stimulation of the thirst center, and polyuria occurs due to an osmotic diuresis. As CNS depression increases in severity, dogs and cats drink less, however the osmotic diuresis continues and results in severe dehydration. Dogs may appear to transiently recover from these CNS signs approximately 12 hours after ingestion.

Phase II: The onset here is approximately 12-24 hours post ingestion and includes symptoms of tachycardia and tachypnea which insidiously tie into the last phase.

Phase III: This develops between 12 and 24 hours in cats and between 36 and 72 hours in dogs. Patients will present with signs and symptoms of oliguric acute renal failure including swollen and painful kidneys on abdominal physical exam, lethargy, anorexia, vomiting, diarrhea, oral ulcers, salivation, tachypnea,

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seizures, coma, and even death.

Laboratory Abnormalities

Within 3 hours of ingestion, as previously mentioned, a distinct anion gap metabolic acidosis develops. Serum osmolality can be increased by as much as 100 mOsm/kg above the normal (280-310 mOsm/kg) range. The difference between measured and calculated osmolality is referred to as the anion gap which is caused by the presence of unmeasured osmotically active particles (ie. ethylene glycol) in the serum. Minimally concentrated urine with an acidic pH as well as calcium oxalate crystalluria is commonly seen as early as 3 hours and 6 hours after ingestion in cats and dogs respectively, with monohydrate calcium oxalate crystals more common than dihydrate calcium oxalate crystals. EG concentrations in serum and urine are detectable by 1 to 2 hours after ingestion. Commercial test kits can detect serum EG concentrations of ≥ 50 mg/dL. Some antifreeze preparations contain fluorescein, which appears bright yellow to green when viewed under a Wood's lamp. Urine fluorescence has been used in EG ingestions in humans and may be useful in veterinary medicine. Acidemia increases the ability of the toxic metabolites to penetrate cells, further depressing CNS function and causing a rapid downward spiral of hypoxia and acidemia.

Diagnosing

Diagnosing ethylene glycol toxicity can be difficult when done purely on the basis of a simple physical exam as it can mimic head trauma, encephalitis, or a generalized drug overdose, so a very involved history needs to be taken as well as conducting a chemistry panel and urinalysis when a patient presents with such symptoms as discussed above in addition to a thorough physical exam giving special attention to the kidneys as they are the organs of primary concern. Make sure the physical exam tests for neurologic components as well such as normal reflexes, righting response, and eye movements (i.e., nystagmus).

Diagnostic Algorithm

1. Assess history, physical exam, neurology exam, and clinical signs

2. Rule out other causes for symptoms
 - a. Household toxins, plants, mushrooms, owner's prescription drugs
 - b. Confirm if there is any chance of EG exposure
3. Preliminary Lab Results (will vary depending on stage of poisoning)
 - a. Chemistry Profile
 - i. Metabolic acidosis with anion gap
 - ii. Hypocalcaemia
 - b. Urine Analysis
 - i. Hypotonic urine
 - ii. Crystalluria
 - iii. Acidic urine pH (normal 7-7.5 dogs, 6.3-6.6 cats)
4. Ultrasound
 - a. Potentially could get a baseline of pet's kidneys on arrival



Treatment Algorithm

Treatment of EG toxicity is aimed at decreasing absorption of ingested EG, increasing excretion of un-metabolized chemical to prevent further metabolism of EG, and correcting the metabolic acidosis that occurs with EG poisoning.

Emesis

Further absorption of EG can be prevented by induction of emesis if animal presents within 1 hour of ingestion.

There are a few way to induce vomiting.

1. Apomorphine: opiate that acts as a potent central dopamine agonist and can be administered 0.03-0.05mg/kg IV or 0.1 mg/kg SQ. It can also be applied directly to conjunctival and gingival membranes and is generally provided as a compounding kit resulting in a 2.5mg/ml concentration after reconstitution since Apomorphine is no longer commercially available. Vomiting usually occurs in 5-10 minutes. If the first dose does not induce emesis, additional doses are not helpful. This medication is most useful in dogs but should not be used in cats.
2. Xylazine: α -2-adrenergic agonist, is

- used as a reliable emetic in cats at a dose of 0.4-0.5mg/kg IV.
3. Syrup of Ipecac: Not currently recommended, though it was once historically. It contains emetine, a toxic alkaloid that produces vomiting by acting as a stomach irritant. It usually produces vomiting in 15-30 min. However, if repeated use fails to induce emesis, then gastric lavage is necessary to remove the emetine to prevent cardiovascular toxicosis and therefore this method for emesis induction is not recommended.
4. Hydrogen peroxide (3%): Stimulates vomiting via the ninth cranial nerve when given in 5-10 mL doses (not more than 2 doses 15 minutes apart) via oral syringe until emesis occurs. However, use cautiously especially in cats, because aspiration of hydrogen peroxide foam causes severe aspiration pneumonia. Repeated doses should be avoided as severe gastric erosion can result.

Activated Charcoal

To further inhibit absorption of EG if it has been ingested within 1-2 hours, administer activated charcoal dosed at 1-4 mg/kg by mouth for granules or 6-12mL/kg by mouth if it's a suspension product. Do NOT administer emetics after charcoal has been given due to risk of charcoal aspiration.

Gastric Lavage

If the product was ingested 2-4 hours previously, then a gastric lavage can be performed.

***Note, once absorption has occurred, these previous methods are futile and instead focus should be placed on increasing excretion of EG via increasing fluid therapy designed to correct dehydration and increase urine production.

Antizol-Vet® (fomepizole)

To prevent metabolism of EG, the activity of alcohol dehydrogenase must be decreased by direct inactivation or by competitive inhibition. The only FDA approved treatment that has this mechanism of action is Antizol-Vet® also known as 4-methylpyrazole or fomepizole. Fomepizole (4-MP) competitively inhibits the rate-determining step of ethylene glycol metabolism which is the enzyme alcohol dehydrogenase. 4-MP effectively inactivates alcohol dehydro

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genase in dogs without the side effects of ethanol and is considered the treatment of choice. The dose is 20 mg/kg IV initially, followed by 15 mg/kg IV, at 12 hour and 24 hour intervals then and 5 mg/kg IV at 36 hr. In cats, 4-MP is ineffective at the canine dosage therefore the recommended dose is 125 mg/kg initially, followed by 31.3 mg/kg at 12, 24, and 36 hours after the initial dose. Continue doses every 12 hours until ethylene glycol is no longer detected. If analysis of ethylene glycol is not available, treat with 31mg/kg every 12 hours through 60 hours. At the time of writing, Antizol® is on backorder and must be compounded as a 1 gram/ml sterile injection by compounding pharmacists capable of providing USP 797 compliant sterile compounds.

Ethanol

When fomepizole isn't available, or if owners can't afford it, the other choice is ethanol as it binds much more easily to alcohol dehydrogenase than ethylene glycol. Because ethanol is the preferential substrate for alcohol dehydrogenase, the presence of ethanol should essentially block metabolism of ethylene glycol. The canine dose for a 20% solution is 5.5ml/kg IV every 4 hours for five treatments then every 6 hours IV for four additional treatments. For cats, 20% ethanol is dosed 5 mL/kg IV and given as a drip over 6 hours for five treatments, and then over 8 hours for four more treatments.

Sodium Bicarbonate

The metabolic acidosis associated with metabolism of ethylene glycol is corrected by administration of sodium bicarbonate. The formula to find the dose is:

$$\text{Bicarb (mEq)} = 0.3 - (0.5 \times \text{body weight kg}) \times (24 - \text{plasma bicarbonate})$$

One-half of this dose should be given IV slowly to prevent overdose, and plasma bicarbonate concentrations should be monitored every 4-6 hours. Additional doses of bicarbonate based on the above formula are frequently necessary. Monitoring urine pH may also be helpful with a goal of maintaining the urine pH be-

tween 7.0 and 7.5 in dogs and 6.3 to 6.6 in cats. The average commercial antifreeze solutions are about 95% EG and the minimum lethal dose of undiluted EG is 1.4 mL/kg body weight in cats and 4.4-6.6 mL/kg in dogs with younger animals being more susceptible. This equates to a few tablespoons in a medium dog or a cat that has merely walked through a puddle and then licked its paw!

Prognosis

The outcome for the dog or cat that has ingested antifreeze varies inversely with the amount of time that has elapsed between ingestion and initiation of treatment as well as the amount ingested. In dogs and cats with azotemia or in oliguric acute renal failure, inhibition of alcohol dehydrogenase is of little benefit because almost all of the EG has already been metabolized. The prognosis for these animals is guarded to poor. Treatment should include correction of fluid, electrolyte, and acid-base disorders and, if possible, establishment of diuresis. Usually, 12 to 24 hours post ingestion, drugs are of little value because the EG has already been metabolized in the body and ethanol or fomepizole should not be used in anuric patients because the unmetabolized EG will not be eliminated and therefore it is a waste of financial resources.

Role of Veterinary Pharmacist

With Antizole Vet® not currently available, pharmacists must be able to correctly compound via USP 797 standards, either 4-methylpyrazole 1gram/mL sterile injection (fomepizole) or, the proper 20% IV ethanol dose for their animal patients. On the other hand, pharmacists can use allegation to create 5% or 7% IV solutions depending on the strength of ethanol used (i.e. 40% is 80 proof) then diluting in appropriate IV solution such as LRS or D5W. Pharmacists must also provide instructions on how to safely administer this compound with the correct weight based dosing over the correct CRI time as mentioned above and include the use of an in-line filter. Pharmacists also have the unique ability to increase public awareness regarding ethylene glycol poisoning. Most owners do not realize the life-threatening severity of anti-freeze ingestion and recommending propylene glycol-based antifreeze should be encour-

aged in areas with animals (or children) nearby. To reduce accidental pet ingestions, owners should be encouraged to use bottles with child proof lids, store bottles safely away from pets (and children), and avoid leaving free fluids in the open by cleaning up spills ASAP. In a retail setting if a panicked owner comes in and requests an over-the-counter treatment for their pet, be perceptive and ask further questions regarding symptoms and risk of possible EG exposure. If EG exposure is a risk, advise that they immediately seek the help of their veterinarian and instill upon them how urgent the situation is! If the situation occurs after hours, as the pharmacist you are able to remain calm and offer to locate the closest Emergency Vet and even call them so they are prepared in advance for the sick animal's arrival.



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