TREATMENT OF ACUTE RENAL FAILURE

Ethylene glycol toxicosis causes acute renal failure!! Fluid diuresis and correction of acidosis are an important parts of therapy. Prognosis is good with early aggressive treatment (<8 hours of ingestion) with 4MP, but poor or grave with prolonged untreated exposure.

The total volume of intravenous fluids needed can be calculated using the equation: Maintenance (40 - 60 ml/kg/day) plus Deficit in L (% dehydration * kg body weight) plus insensible losses from vomiting and/or diarrhea. Deficit amounts can be infused rapidly, but so that fluids have time to equilibrate between the vascular, interstitial, and cellular compartments, maintenance fluids must be divided and administered over 8–12 hours. A balanced electrolyte solution can be used (LRS, Normosol); however, if hyperkalemia exists, 0.9% saline should be substituted.

Due to the reduced ability of the kidneys to regulate fluids, Ethylene Glycol renal failure patients are at a high risk for overload and death. If oliguric renal failure occurs, Furosemide, a loop diuretic, has experimentally been shown to increase urine production, dislodge tubular obstructions, and induce vasodilatation. [13] Often it is given as a bolus (2–4 mg/kg), and if urine production increases, a CRI is started (0.25–1.0 mg/kg/h). An indwelling urinary catheter should be aseptically placed to measure urine output. Hourly urine output is then used to determine "maintenance" fluid rate.

Metabolic Acidosis occurs about 12 hours after EG ingestion and lasts up to 24 hours. Severe metabolic acidosis leads to compensatory respiratory alkalosis. Laboratory abnormalities include increased anion gap, decreased serum bicarbonate, and hyperglycemia. Generally, it is not treated unless serum bicarbonate is <14 mEq/L or pH <7.2. A conservative bicarbonate dose can be calculated: (bodyweight in kg x 0.3) x (16 - measured bicarbonate

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ETHYLENE GLYCOL TOXICITY

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Consider this situation: You are presented with a small outside dog that over the last few hours became wobbly and ataxic. The dog is in good flesh and has no history of medical problems. In questioning the dog's owner about any possible ingestion, you ascertain that the owner had been adding antifreeze to the car and the dog was outside with him, but he didn't see the dog lap any up. Could this be antifreeze toxicity?

On examination, there are decreased neurological reflexes and the dog seems very depressed. CBC and chemistry profile show normal parameters. What's next? You have an ethylene glycol test available and it shows a slight positive. Should you administer ethanol or 4MP antidote treatment? Most EG ingestions are not witnessed by the pet owner!! If there is any suspicion of EG toxicity, treatment should begin immediately.

This is a confusing dilemma. Did the dog get a little antifreeze and the test is showing only slight positive? Had the dog ingested the antifreeze over 8 - 10 hours ago and much of the ethylene glycol has been metabolized? What do you do next? The answer lies in the ability to determine if there is oxalate in the blood! There is a new dual test kit from Kacey Diagnostics to determine both ethylene glycol and serum oxalate. That will tell you if there is a small ingestion, in which case there will be no oxalate, or if the oxalate test is positive, ethylene glycol has been metabolized to oxalate and there will be kidney damage.

If there is a strong positive ethylene glycol test and a negative oxalate test, the ingestion was recent and antidote treatment with 4MP will be effective. If the ethylene glycol test is positive and the oxalate test is positive, then the ingestion occurred 8-10 hours ago and antidote treatment may help, but it may be too late, since calcium oxalate crystals will be deposited in the kidneys resulting in acute renal failure. If the ethylene glycol test is negative, but the oxalate test is positive, then there is little chance that the antidote treatment will help.

Let's investigate what we know about ethylene glycol ingestion, testing, and treatments.

Ethylene glycol (EG) is a sweet tasting organic solvent found in many automotive products including antifreeze and brake fluid. EG is rapidly absorbed after ingestion and in the dog it reaches peak plasma concentration in 2 hours.[1] In cats the peak plasma level occurs within 1 hour. [2] The published lethal dose of pure EG in cats is 1.5 ml/kg and in dogs it is 4.4-6.6 ml/kg of body weight. [3] Antifreeze is diluted with water before use in automobiles. In cats, EG glycol toxicity is very rapid probably due to the ineffective elimination of metabolites. EG ingestion in dogs and cats may result in acute intoxication resulting in death.

Clinical signs of EG toxicosis occurs in stages in the dog. In the first stage (30 min - 12 hrs. post ingestion) central nervous system signs predominate (depression, ataxia, seizures, coma or death) and cardiopulmonary signs (such as tachypnea or tachycardia) may result from pulmonary edema. [4] After 24 - 72 hours post ingestion, oliguric renal failure results from deposition of calclum oxate monohydrate (COM) crystals in the renal tubules. This can occur as fast as 12 hours after ingestion in some cats.

Urine sediment If EG ingestion is not diagnosed and treated early, it carries a grave prognosis. In dogs, if EG ingestion is identified and treatment is begun within 8 hours of ingestion, the prognosis is much better. In cats, treatment within 3 hours of ingestion can be beneficial. It has been reported that the mortality after ingestion of EG is 96-100% in cats and 59-70% in dogs.[5]

The metabolism of ingested EG by the hepatic enzyme alcohol dehydrogenase (ADH) results in the production of glycolaldehyde, glycolic acid, glyoxylic acid and oxalic acid. These metabolites are cellular toxins that can cause cardiopulmonary failure, life threatening metabolic acidosis, central nervous system depression, and kidney failure. [6] Recent studies have shown that of these metabolites, only the COM crystals are responsible for the kidney failure (from precipitation of COM crystals in renal tubular epithelial cells and around the kidney tubules resulting in necrosis). [7]

ETHYLENE GLYCOL TESTING

EG ingestion tests for in-office use include the VetSpec EG Qualitative Reagent Test Kit and an EG Rapid Strip Test by Kacey Diagnostics. In a recent comparison of the point of care test kits from VetSpec and Kacey, the Kacey EG Test strips had a 100% sensitivity and specificity compared to the VetSpec, which had a 65 to 95% sensitivity and a 40-70% specificity. [8] The Kacey EG Test strips are much easier to use, requiring only 20 microliters of serum placed on a pad that displayed a green color intensity correlating to serum concentrations of EG at 20mg/dl (lethal dose for cats), 50 mg/dl (lethal dose for dogs), and 75 mg/dl within 10 minutes. A low positive EG test (<20 mg/dl) in cats may be the result of reaction with organic chemicals (e.g.; alcohols, toxaban) in the plasma other than EG.[9]

A new, unique addition to the diagnostic tests used for prognosis in EG ingestion is the plasma oxalate test. High plasma oxalate levels make the 4MP EG antidote Fomepizole less likely to have the desired effect because EG metabolism has already occurred. High oxalate levels in the plasma also indicate a higher chance of COM crystals precipitating in the kidneys. The Kacey Diagnostics Antifreeze Oxalate Test strips combine the oxalate oxidase reaction and color reaction in one step on a pad on the strip using a 10 microliter plasma sample. This test provides a qualitative measurement of Oxalic Acid 8-10 hours after EG ingestion. After exactly 5 minutes of plasma saturation, the intensity of the product color development on the test pad is read from a chart and is directly proportional to the oxalate concentration in the sample.

Combining the information from the EG test and the Oxalate test aids in determining the prognostic outcome:

EG Test	Oxalate Test	Prognosis
POSITIVE (+)	NEGATIVE (-)	Treat with 4MP - GOOD
POSITIVE (+)	POSITIVE (+)	Treat with 4MP - Fluids GUARDED
NEGATIVE (-)	POSITIVE (+)	Do not use 4MP - **POOR**

ETHYLENE GLYCOL TREATMENTS

The treatment of acute ingestion of EG requires the prevention of the EG metabolism. This is accomplished by preventing the alcohol dehydrogenase (ADH) enzyme from breaking down the ethylene glycol into its toxic metabolites. By competing for the ADH enzyme these antidotes slow the rate of metabolite production and allow the liver to process and excrete them as they are produced.

Two antidotes for achieving this goal include intravenous ethanol and intravenous 4-methylpyrazole (4MP), which has a much higher binding affinity for the ADH enzyme. Ethanol and 4MP should not be used simultaneously!

4MP is very effective in dogs if administered within 8 hours of ingestion, but in cats a much higher dose is required, resulting in more severe side effects from the drug. Ethanol is much less costly than 4MP. In cats, either treatment must be given within 3 hours of ingestion to have any chance of survival.

ETHANOL ANTIDOTE

In dogs, ethanol can be administered at 8.6 ml/kg (600mg/kg) bolus of a 7% ethanol solution (70 mg/ml) and then maintained at a constant rate infusion of 1.43 ml/kg/hr (100 mg/kg/hr) over 48 hours.[10]

- To make 1 Liter of 7% solution using 80 proof vodka, remove 175 mL of saline from the 1 Liter 0.9% saline bag and replace with 175 mL of vodka.

- To make 1 Liter of 7% solution using 190 proof grain alcohol (Everclear), remove 73 mL of saline from the 1 Liter 0.9% saline bag and replace with 73 mL of grain alcohol.

For cats, use a 5% ethanol intravenous solution (50 mg/ml) as a constant rate infusion of 5ml/kg/h (250 mg/kg/hr) for 48 hours or longer.[3] To make 1 Liter of 5% solution using vodka, remove 125 ml of saline from the bag and replace it with 125 ml of 80 proof vodka. Cats must be maintained in a warm environment to prevent hypothermia.

4MP (FOMEPIZOLE) ANTIDOTE

Add 28.5 ml of sterile saline to the Fomepizole 1.5 g bottle and shake thoroughly. That will make a final concentration of 50 mg/ml. One 30 ml bottle should be sufficient to treat up to a 75 pound dog. This solution is stable for 72 hours.

For treating EG ingestion, an initial loading dose of 20 mg/kg should be administered intravenously slowly over 5-10 minutes as soon as EG ingestion is suspected. [11] After 12, 24, and 36 hours, additional doses of 15 mg/15 mg/kg and 5 mg/kg should be administered intravenously slowly. If the EG test is still positive at 36 hours, administration of 4MP can be continued at 5 mg/kg every 12 hours until the EG test is negative or the dog has recovered. The cat dose is 125 mg/kg intravenously initially, followed by IV infusions of 31.25 mg/kg at 12, 24, and 36 hours. [12] Fomepizole must be given to cats within 3 hours of ingestion to be effective..