

Ethylene glycol poisoning



Ethylene glycol poisoning is extremely serious in cats. A small dose can result in signs which are initially non-specific and may be easily missed. Ethanol is the antidote to ethylene glycol toxicity and works by preventing metabolism to toxic compounds. However, it is generally only worthwhile if started within a few hours of ingestion. Although a potentially lethal dose of ethylene glycol can be survived if treatment is prompt, many cats with ethylene glycol poisoning present late and as a result most cases have a fatal outcome.

Ethylene glycol (also known amongst other names as ethanediol) is a common ingredient of antifreeze; it is also found in some screenwashes or more rarely de-icers (Figure 1). Most antifreezes contain ethylene glycol (or occasionally methanol), and are liquids which are added to water in engine radiators to prevent freezing and improve cold weather performance. The usual final dilution is approximately 1:1.

Exposure

Cats may be exposed by drinking neat antifreeze from a spill, but are more commonly exposed after drinking the diluted fluid from drained vehicle radiators. Most exposures are not witnessed.



Figure 1:
Ethylene glycol is highly toxic to cats



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Key point

As with many poisoning cases in cats, ingestion is rarely witnessed.

Prevention by informing owners of the dangers of leaving antifreeze around is far preferable, as mortality from ingestion is high.



Mechanisms of toxicity

The major toxic agent in ethylene glycol poisoning is not the parent compound but the metabolites produced by the action of alcohol

dehydrogenase (Figure 2). This enzyme oxidises ethylene glycol to glycoaldehyde. This is then metabolised to glycolic acid which appears to be the principle cause of the acidosis observed with ethylene glycol toxicity. Further metabolites of glycolic acid are glyoxylic acid and then oxalate; the latter causes renal damage and hypocalcaemia by binding to calcium to form calcium oxalate (crystals of which may be present in urine).

Toxicokinetics

Ethylene glycol is rapidly absorbed from the gastrointestinal tract; in cats the peak plasma concentration occurs about 1 h after ingestion and the urine concentration peaks about 3 h after ingestion.¹

Toxic dose

Cats are more susceptible to ethylene glycol than dogs and signs progress more rapidly, but it is not clear why. It may be that toxic metabolites are eliminated more slowly, or metabolites are metabolised more rapidly to other more toxic compounds.¹

The lethal dose of ethylene glycol in cats is commonly reported as 1.5 ml/kg.² In another study 1 g/kg (where 1 ml is approximately 1 g) was fatal to cats within 48 h, whereas this dose did not affect rats, rabbits or guinea pigs.³ Undiluted ethylene glycol-containing antifreezes generally contain 95% or more, with 'ready to use' products being approximately 50%.

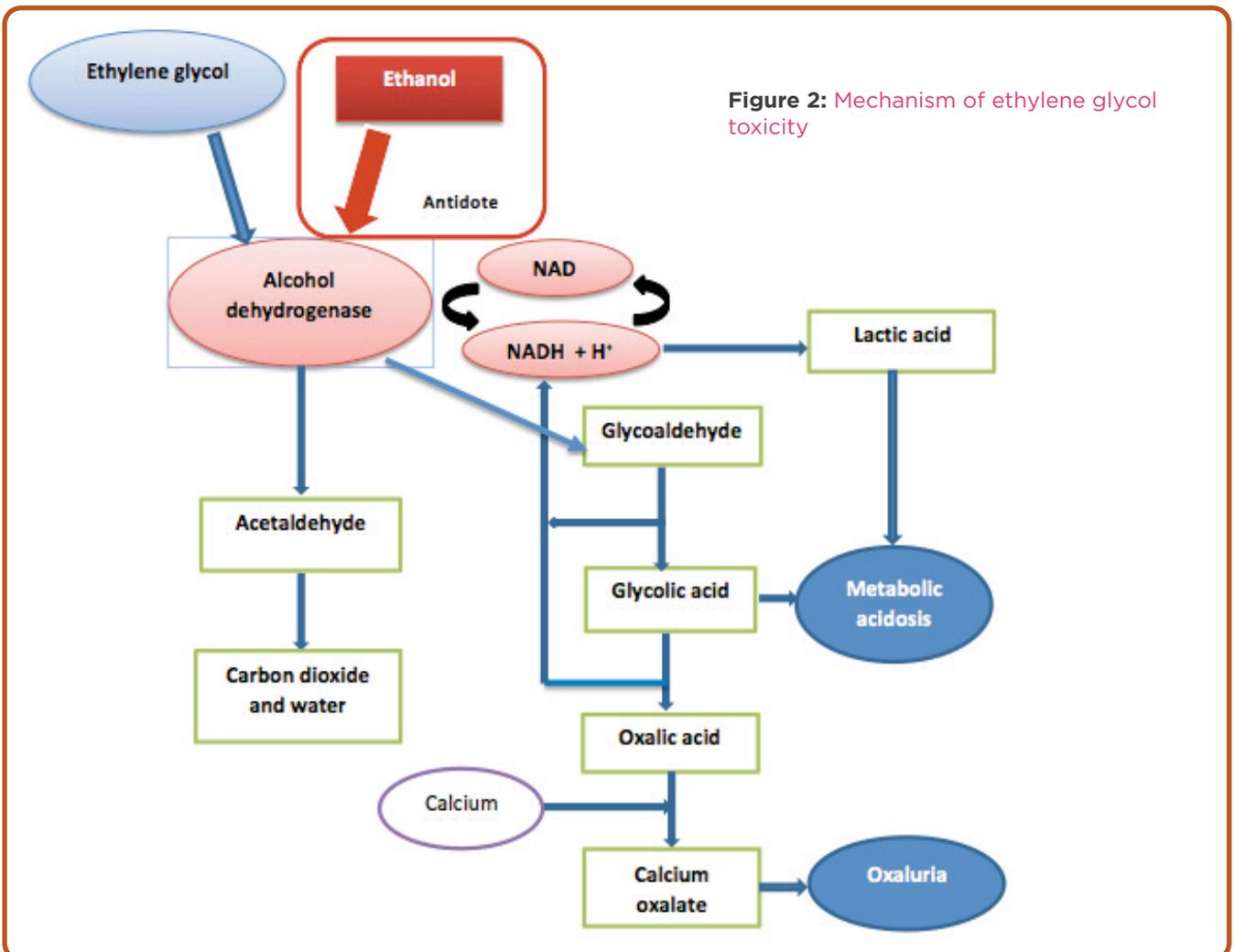


Figure 2: Mechanism of ethylene glycol toxicity

How the antidotes work

The aim of antidotal therapy in the management of ethylene glycol toxicosis is to prevent formation of the toxic metabolites (Figure 2). This is achieved through administration of ethanol or fomepizole (4-methylpyrazole, 4-MP), both of which are competitive inhibitors of alcohol dehydrogenase, with a higher affinity for the enzyme than ethylene glycol. Fomepizole is the more potent inhibitor. Inhibition of ethylene glycol metabolism allows time for renal excretion of the unchanged parent compound.

In the study by Connally et al,⁴ cats only survived lethal doses of ethylene glycol if treated with fomepizole or ethanol at or before 3 h. In an earlier study, of nine cats given lethal doses of ethylene glycol (4, 6 or 8 ml/kg) and treated with ethanol at 4 h, five (55.5%) survived compared to only one (8%) survivor of 12 cats treated at 8 h.⁵ These studies therefore suggest that survival is most likely in cats if treatment with ethanol or fomepizole is started within 3–4 h of ingestion.

Fomepizole is effective in cats but the drug is expensive and the cost of treatment in cats is increased further because they require a much higher dose (6 x dose) than dogs or humans. In addition, this high dose causes sedation, ataxia and hypothermia in cats.⁴ As a result ethanol is more commonly used and is much more readily available.

Clinical signs

In the early stages of ethylene glycol poisoning, which occurs from 30 minutes to 12 h, there are central nervous system signs due to unmetabolised ethylene glycol. These include vomiting, ataxia, tachycardia and weakness. These

Key point

The longer the time between ingestion and treatment, the poorer the prognosis. If acute kidney injury has occurred then the prognosis is poor.



early signs may be easily missed, particularly in an outdoor cat. Polyuria, dehydration, tachypnoea, acidosis and hypothermia may occur. Polydipsia, although common in dogs, is generally not seen in cats. Convulsions can occur at this stage in severe cases.

From 12–24 h cats remain depressed and develop cardiopulmonary signs with tachypnoea, tachycardia, acidosis, hyper- or hypotension, pulmonary oedema, arrhythmias, congestive heart failure and circulatory shock. Cerebral oedema may occur. Death can occur at this stage in some cases.

Renal system signs including oliguria, azotaemia and/or uraemia develop and the renal impairment exacerbates acid/base and electrolyte disturbances. Kidneys may be swollen and painful and there may be vomiting, anorexia, oral ulcers, severe depression, lethargy, coma and convulsions due to uraemia.⁶

Laboratory changes

There is raised urea and creatinine, which is generally seen from about 12 h in cats,⁷ low urine specific gravity (due to osmotic diuresis induced by ethylene glycol), proteinuria, glucosuria, haematuria and albuminuria. Calcium oxalate crystals can appear in the urine within 3 h of ingestion (Figure 3),⁴ but the absence of oxalate crystals does not

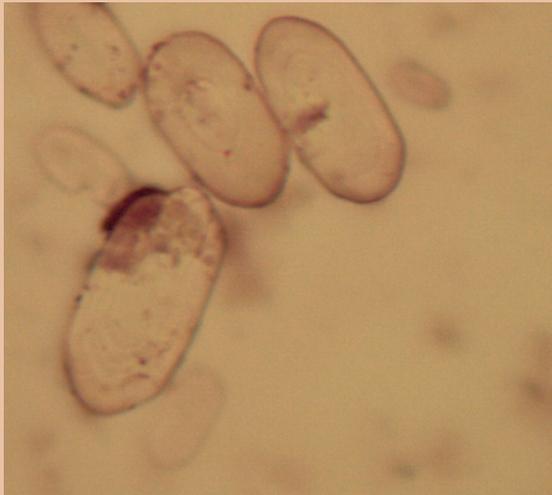


Figure 3: Calcium oxalate monohydrate crystals (x500 magnification, Kovastain): in this image the crystals have a rounded ovoid appearance but they can be more hexagonal (picture courtesy of Kathleen Tennant)

Key point

Cats with ethylene glycol toxicity may have calcium oxalate monohydrate crystals in their urine but the absence of these crystals does not rule out poisoning.



rule out ethylene glycol poisoning. There may also be hyperglycaemia, hypocalcaemia (due to binding of calcium to oxalate), hyperphosphataemia and hyperkalaemia (due to acute kidney injury and acidosis). Clinical signs of hypocalcaemia generally do not occur in ethylene glycol poisoning because of the shift to the active, ionised form of calcium when metabolic acidosis occurs.^{6,8}

There is acidosis, typically with a blood pH of <7.3 and acidic urine with a pH <6.5.⁹ The blood pH and plasma bicarbonate are decreased

by 3 h after ingestion, and markedly decreased by 12 h.⁷ Neutrophil leukocytosis may also be observed.⁶

Prognosis

Prognosis should be based on an animal's response to treatment,⁹ but the longer the time to treatment the less favourable the prognosis. Recovery may take 3–5 days if treated aggressively within a few hours of ingestion,⁴ but in most cases unless the ingestion was witnessed, animals usually present in the final stage of poisoning. Coma or acute renal injury indicates a poor prognosis.

In a study of 25 cases of ingestion of ethylene glycol in cats the mortality rate was 96%.¹⁰ In another report of 26 cats and 24 dogs with ethylene glycol poisoning only six animals (12%) survived. Half of the survivors were admitted within 12 h.⁶ In a review of all fatal cases of poisoning reported to the Veterinary Poisons Information Service (VPIS) the most common agent to result in a fatal outcome in cats was presumed to be (few cases had laboratory confirmation) ethylene glycol. Of 213 cats with suspected or confirmed ethylene glycol poisoning with known outcome, 38 died (17.8%) and 159 were euthanased (74.6); this is an overall fatality rate of 92.5%.¹¹

Diagnosis

Diagnosis is generally based on history, clinical signs and laboratory findings. Ethylene glycol poisoning should be suspected in any animal with acute onset of signs, raised urea, creatinine and low urine specific gravity.⁹

Test kits are available for confirming ethylene glycol in blood but they have some limitations. Cats can be poisoned at concentrations below that detected by the kits (usually

500 mg/l) and some kits also give false positives in the presence of alcohol (such as ethanol). These kits only detect ethylene glycol not its metabolites. Therefore, in late presenting animals the test may be negative because the ethylene glycol has been metabolised or is below the limit of detection.

Many antifreeze products contain fluorescein (a green or red dye depending on the pH of the medium), which fluoresces under ultraviolet light. Sometimes the dye may be detected in urine or vomitus using a Wood's lamp and examination of the paws, mouth and face may be useful.¹² However, this is not a reliable test,¹³ as it is difficult to detect fluorescence in a test sample without a positive and negative control for comparison.¹⁴

Treatment

The aim of therapy in ethylene glycol poisoning is to prevent metabolism and the production of toxic metabolites, reverse electrolyte and acid/base disturbances and maintain the glomerular filtration rate. Advice should be sought from a poisons information service and a specialist centre to optimise treatment of affected cats.

Decontamination

Treatment is recommended for any quantity but gut decontamination is probably only worthwhile within 1 h of ingestion. Adsorbents such as activated charcoal are not useful. In most cases cats do not present until the onset of signs, hours after ingestion.

Monitoring, investigations and initial treatment

In symptomatic cats the blood pH, electrolytes and renal function should be monitored. Intravenous fluids (2–3 times maintenance) are

essential to ensure adequate hydration and therefore renal perfusion and to promote diuresis. If possible, the central venous pressure and urine output should be monitored in cats with acute kidney injury because of the risk of fluid overload and subsequent pulmonary oedema. If there is oliguria or anuria, diuretics such as mannitol or furosemide can be given if there is no response to fluid therapy alone. There is a significant risk of volume overload in cats with acute kidney injury and advice on treatment should be taken from a specialist and, ideally, the cat referred to a specialist centre. Peritoneal dialysis or haemodialysis can be used in acidotic cats with oliguria, but are rarely available.

Other treatments may include treatment of hyperkalaemia, management of nausea and vomiting and specific treatment of severe acidosis. Treatment of hypocalcaemia is rarely required.

Antidotal treatment

After ingestion of ethylene glycol the sooner antidotal therapy is started the better the outcome. A potentially lethal dose of ethylene glycol can be survived if treatment is prompt. Survival is most likely if treated within 3–4 h of ingestion. There is no point giving ethanol or fomepizole to block metabolism if the ethylene glycol has been metabolised. Unfortunately, cats

Tip

Antidotes must be given within 3–4 h of ingestion and, unfortunately, there is no point giving them to cats already suffering acute kidney injury.



often present late by which time such antidotal therapy is no longer of use. Management in these cases is supportive/palliative. Antidotes

Box 1: Ethanol regimen for ethylene glycol poisoning

Intravenous dosage

- 5% solution as a constant rate infusion at a rate of 5 ml/kg/h for 48 h or longer

OR

- 5 ml/kg body weight 20% ethanol in saline IV every 6 h for 5 doses then every 8 h for 4 doses.

Ideally, a pharmaceutical grade of ethanol should be used but if not available oral ethanol can be given or an IV solution made up using 40% vodka, as follows:*

- **To make a 5% solution:** add 125 ml of vodka to 875 ml of IV fluid lactated Ringer's or saline, that is remove about 125 ml from the bag and replace with vodka. An in-line filter should be used for the IV.

To make a 20% solution: dilute an equal volume of vodka with IV fluids such as lactated Ringer's or saline (eg, 500 ml with 500 ml). An in-line filter should be used for the IV.

Oral dosage

- 2.4 ml/kg orally of a 40% solution (eg, vodka, whisky, suitably diluted; equated to 750 mg/kg) over the first hour, followed by 0.5 ml/kg/h (equates to 150 mg/kg/h).

This is best given via an indwelling nasogastric tube, periodically over the treatment period (that is, not all at once, as it is irritant and could result in vomiting).

*From Plumbs (2008)¹⁵

should not be used in cats with acute kidney injury as antidotes increase the half-life of ethylene glycol and if renal damage has already occurred the kidneys may not be able to effectively eliminate it.

Ethanol is the most readily available and commonly used antidote for ethylene glycol toxicity (Box 1). It can be given orally or intravenously but use of a constant rate infusion is preferred as it will result in more stable blood ethanol concentration.⁴ The dose of ethanol required will cause significant central nervous system (CNS) depression and hypothermia. Nursing care for a recumbent patient will be required. Ethanol may also worsen acidosis and can cause hypoglycaemia. The blood glucose should be monitored every 4–6 h, because of the risk of hypoglycaemia.⁷ The airway should be protected if there is significant CNS depression. If the cat survives it will be depressed and lethargic (that is, hung over) during recovery from ethanol therapy and require further supportive care (eg, nutritional support and fluid therapy).

Conclusions

Ethylene glycol ingestion is commonly lethal in cats, but prompt diagnosis and treatment with ethanol therapy can be life-saving. In many cases, however, the early signs may be missed or vague and non-specific resulting in late presentation. Clients should be educated on avoiding exposing cats, for example, in the garage.

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Many cases of poisoning are preventable by raising owner awareness, one of the aims of the Keeping Cats Safe Campaign. The Campaign is run by International Cat Care in conjunction with the Veterinary Poisons Information Service and Agria Pet Insurance. For more information see: <http://icatcare.org/keeping-cats-safe>

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