Ethylene glycol toxicity

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ABSTRACT: Ethylene glycol (EG) poisoning continues to be common. This article covers the metabolism of ethylene glycol, clinical signs of toxicity and establishing a diagnosis of EG poisoning, as well as the emergency management of patients with suspected or identified ingestion and the associated prognosis.

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Helen qualified as a veterinary nurse in 2000, went on to gain a Certificate in Small Animal Nutrition and then competed the RCVS Diploma in Advanced Veterinary Nursing (Surgical) in 2005. She is particularly interested in emergency and critical care and is currently studying for the Vets Now Certificate in Emergency and Critical Care. Having gained a wealth of experience in both first-opinion and referral nursing over the past 16 years, Helen now enjoys her position as a senior nurse at the Animal Health Trust.
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What is ethylene glycol?

Ethylene glycol (EG) is the most common ingredient in antifreeze, but is also found in other vehicle maintenance solutions (such as hydraulic brake fluid and de-icer), photographic solutions and industrial solvents.

EG is an odourless, colourless, sweet and palatable liquid. Due to its palatability, some states in the USA require a bitterant to be added; unfortunately, this is currently not a requirement within the UK. As the minimum lethal dose is 6.6 ml/kg for dogs and just 1.4 ml/kg for cats (Bischoff, 2014), mortality rates are high (cats: 97%; dogs: 59–70%). Numbers of EG toxicity cases peak when antifreeze is used the most: late autumn and early spring (Poppenga, 2007).

What happens when EG is ingested?

After being absorbed rapidly by the stomach and gastrointestinal tract, EG is metabolised primarily by the liver into glycolic acid, which causes metabolic acidosis, and then finally it is processed into several metabolites, one of which is oxalic acid. Oxalic acid binds to calcium ions in the renal tubules and other tissues to form calcium oxalate (Bischoff, 2014).

This results in hypocalcaemia, the obstruction of the renal tubules and renal epithelial damage, leading to acute kidney injury and ultimately multiple organ failure.

Clinical signs

Clinical signs depend on both the amount of EG ingested as well as the time since it was ingested. They occur in three phases (**Table 1**).

Diagnosis

As prognosis decreases dramatically with any delay in treatment, a diagnosis must be rapidly made, or assumed:

- Patient history – if the patient has been seen lapping products which contain EG, or is at risk of potential exposure (such as having access to a garage), treatment should be initiated without delay.
- Woods lamp: some antifreeze products have fluorescent dye added to them which is visible around the mouth, in vomit and in urine when examined under a Woods lamp.
- A minimum database including biochemistry, haematology, acid–base evaluation (through blood gas and electrolyte analysis) and urinalysis should be performed. Depending upon the clinical phase at the time of presentation, this might identify hypocalcaemia, azotaemia, metabolic acidosis and an increased anion gap.
- Urine cytology can be helpful in identifying both acute renal tubular injury and the presence of calcium oxalate monohydrate crystals (coffin-shaped), which commonly accompany this specific toxicity (**Figure 1**).
- Confirmatory tests include commercial test strips (Kacey diagnostics). It is important to remember that these may cross-react with other compounds found in pet foods and other products (such as glycerol, ethanol, sorbitol or propylene glycol).
- Several laboratories in the UK can perform tests to detect EG, although the turnaround for these results is likely to be such that it is only possible to gain retrospective confirmation of exposure.

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Table 1. Clinical signs

Stage/Phase	Time from ingestion	Clinical signs	Prognosis
1	1 to 4 h	Vomiting	Excellent
		Polyuria/polydipsia	
		Ataxia	
		Depression	
2	4 to 6 h	Signs of metabolic acidosis; cardiopulmonary: tachypnoea, tachycardia, pulmonary oedema; CNS signs: depression, hypothermia, coma	
3	24 to 72 h	Acute renal failure, oliguria, anuria, oral ulcerations, salivation, vomiting, anorexia, seizures, large painful kidneys on palpation	Poor

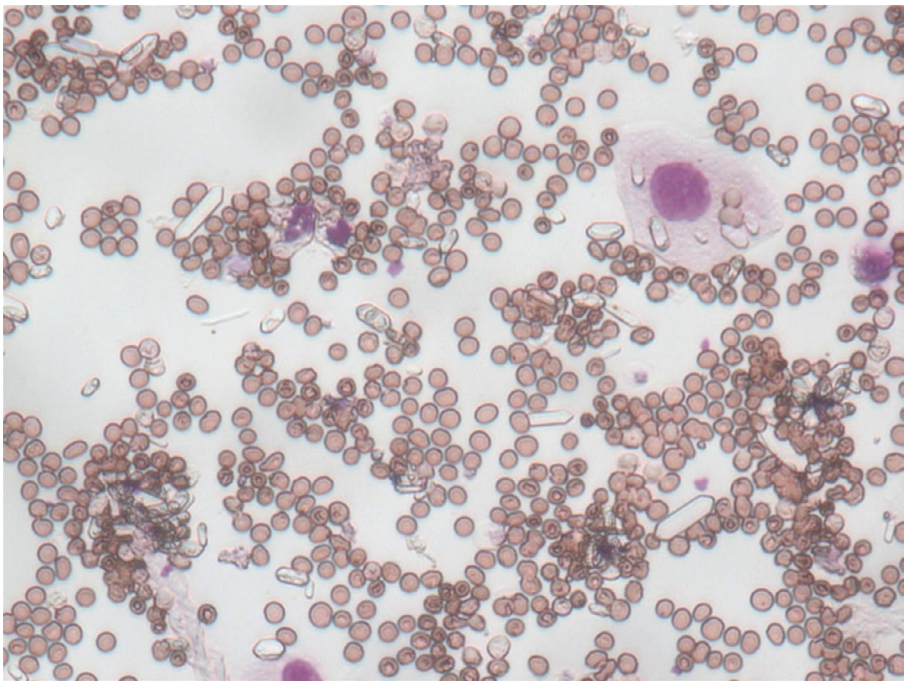

Figure 1. Calcium oxalate monohydrate crystals
Courtesy of Francesco Cian, Batt Laboratories, UK

Emergency management

In order to improve outcome, emergency management is best initiated as soon as possible following a known or suspected exposure to EG, and even while a diagnosis is being established.

On admission, the patient should be weighed (to enable drug and fluid doses to be calculated accurately), an intravenous catheter should be placed and blood samples collected. In the depressed patient oxygen by mask or flow by should be initiated and it may only be possible to sample blood from the catheter hub for PCV/TS and electrolytes; particular attention should be paid to evaluating the anion gap and serum osmolality. Where possible, it is important to determine calcium levels and urea and creatinine. Azotaemia is considered a negative prognostic indicator, and typically indicates that treatment is unlikely to be successful.

Fluid therapy should be initiated to correct dehydration, metabolic acidosis, electrolyte imbalances and to promote diuresis (Bischoff, 2014). An isotonic crystalloid such as Lactated Ringers should be infused at twice maintenance (Richardson & Gwaltney-Brant, 2009). In the anuric patient respiratory rate and depth should be monitored regularly to identify development of pulmonary oedema while they are receiving fluid therapy.

Box 1. Anion gap:

The most common causes of metabolic acidosis with a high anion gap (AG) are diabetic ketoacidosis, uraemia, ethylene glycol toxicity and lactate. Normochloraemic metabolic acidosis is characterised by a reduction in bicarbonate, a low pH and normal chloride values.

AG can be calculated using blood gas and electrolyte analysis and the following formula for all patients:
$AG = (Na^+ + K^+) - (Cl^- + HCO^{3-})$

The normal AG concentration is approximately 12–24 mEq/l in dogs and 13–27 mEq/l in cats (Kaae & de Morais, 2008).

The phase of toxicity (see **Table 1**) should be identified and the patient should be observed carefully to identify any change in their condition. The patient's vitals including heart rate, pulse quality, respiratory rate, temperature and mentation should be monitored and recorded every 30 min. Urine output and concentration should be monitored every 4 h. Serial monitoring of electrolytes should be performed according to the veterinary surgeon's directions. Non-invasive blood pressure (either Doppler or oscillometric) and electrocardiogram (ECG) should be made available and used as required.

Gastrointestinal decontamination

The aim of gastrointestinal (GI) decontamination is to remove EG and its metabolites from the patient before they are converted into oxalic acid (Palm & Kanakubo, 2015). As EG is rapidly absorbed, GI decontamination is futile unless ingestion has been very recently witnessed. In this circumstance emesis can be induced with apomorphine within an hour. In cats, apomorphine may not be as effective at inducing emesis; therefore, an alpha-2-agonist such as dexmedetomidine or xylazine may be administered intramuscularly (Willey, Julius, Claypool, & Clare, 2016). Activated charcoal can then be given to absorb residues, although its effectiveness is controversial (Richardson & Gwaltney-Brant, 2009).

Antidotes

The metabolism of EG to toxic metabolites can be inhibited by the administration of an antidote such as ethanol or fomepizole (4-methylprazole). While antidotes are best administered as soon as possible after ingestion, it is still

Figure 2. Plain vodka can be used in an emergency

worthwhile giving them up to 32 h after exposure (Bischoff, 2014). Although fomepizole is the preferred antidote, and causes less CNS depression than ethanol, its poor availability and high cost are prohibitive (Aldridge & O'Dwyer, 2013).

If medical-grade ethanol is not readily available plain vodka can be used in an absolute emergency (a constant rate infusion of 1.25 ml/h can be used for up to 72 h) (**Figure 2**) (Thompson, 2012)

Ethanol will cause respiratory and CNS depression; therefore, patients receiving this treatment need close and continuous monitoring and may require intubation and care of the airways.

Hypocalcaemia

Hypocalcaemia is reported in EG poisoning cases due to calcium oxalate crystal formation (Bischoff, 2014). Clinical signs include seizures, weakness, ataxia, anorexia, vomiting, arrhythmias and muscle tremors. Hypocalcaemia can be confirmed by electrolyte analysis.

If the patient has clinical signs and is found to have a decreased ionised calcium concentration, calcium gluconate should be given very slowly (over at least 10 min) intravenously. An ECG should be used to monitor the patient during administration and the infusion should be discontinued if the patient becomes bradycardic.

Advanced therapies

If the patient is not responding to conventional medical treatment, advanced therapies such as peritoneal dialysis (PD), intermittent haemodialysis (IHD) or continuous renal replacement therapy (CRRT) may be considered in order to reduce the risk of life-threatening acute kidney injury (AKI).

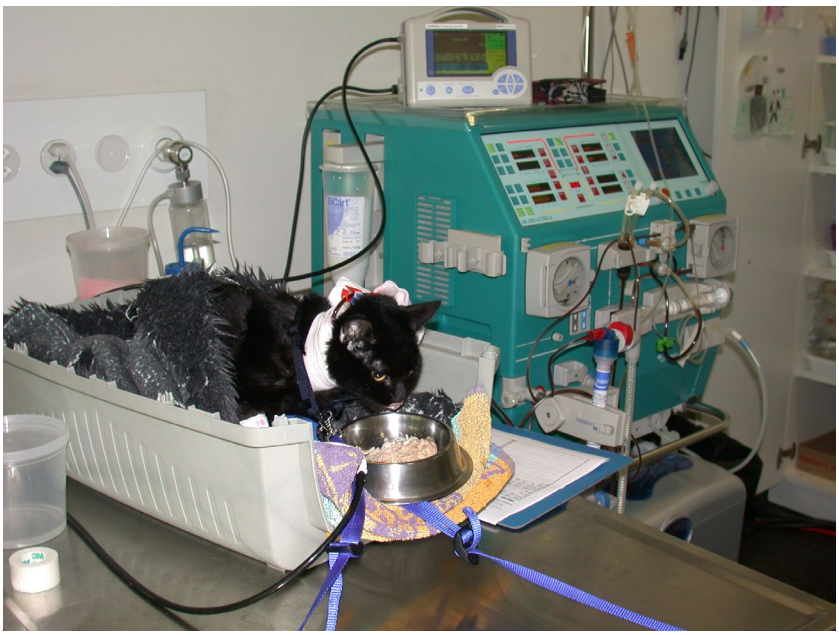

Figure 3. Cat receiving haemodialysis
Courtesy of Fabiane Buser

Peritoneal dialysis

"Dialysis is defined as the transfer of water and solute from one compartment to another across a semi-permeable membrane" (Welsh & Labato, 2012).

Peritoneal dialysis (PD) uses the peritoneum as the semi-permeable membrane between the peritoneal cavity and the blood in the peritoneal capillaries.

"The primary indication for PD in animals is acute kidney injury (AKI) to correct water, solute and acid base abnormalities and to remove ureamic toxins" (Ross & Labato, 2013) and is further indicated by oliguria which is unresponsive to fluid therapy.

PD is known to help reduce blood levels of ethylene glycol as well as urea, creatinine and potassium (Aldridge & O'Dwyer, 2013). As risk of infection and complications outweigh the benefit of this treatment, it should, however, be considered a last resort if azotaemia fails to improve despite treatment. PD is less effective than extracorporeal therapy renal replacement therapies. PD does not require specialist facilities or equipment, but is labour-intensive and requires close patient monitoring (Bexfield & Lee, 2014).

Extracorporeal therapy renal replacement therapy

Renal replacement therapy (RRT) has evolved over the past 40 years to become the management method of choice for AKI and acute poisoning cases. RRT is known to be safe and effective for patients ranging from just 1.5 to 600 kg (Cowgill & Guillaumin, 2013). There are two types of RRT currently used: intermittent haemodialysis (IHD) and continuous renal replacement therapy (CRRT). Unfortunately, access to RRT is restricted as it is only available at some referral institutes (**Figure 3**).

Box 2. Continuous renal replacement therapy

"CRRT is a blood purification modality that uses a combination of convection and diffusion to eliminate uremic toxins and correct electrolyte imbalances" (Acierno and Maeckelbergh, 2008). CRRT more closely approximates normal kidney function and continues until normal kidney function is restored.

CRRT:

1. A jugular catheter is placed and blood is diverted from the patient to the CRRT unit.

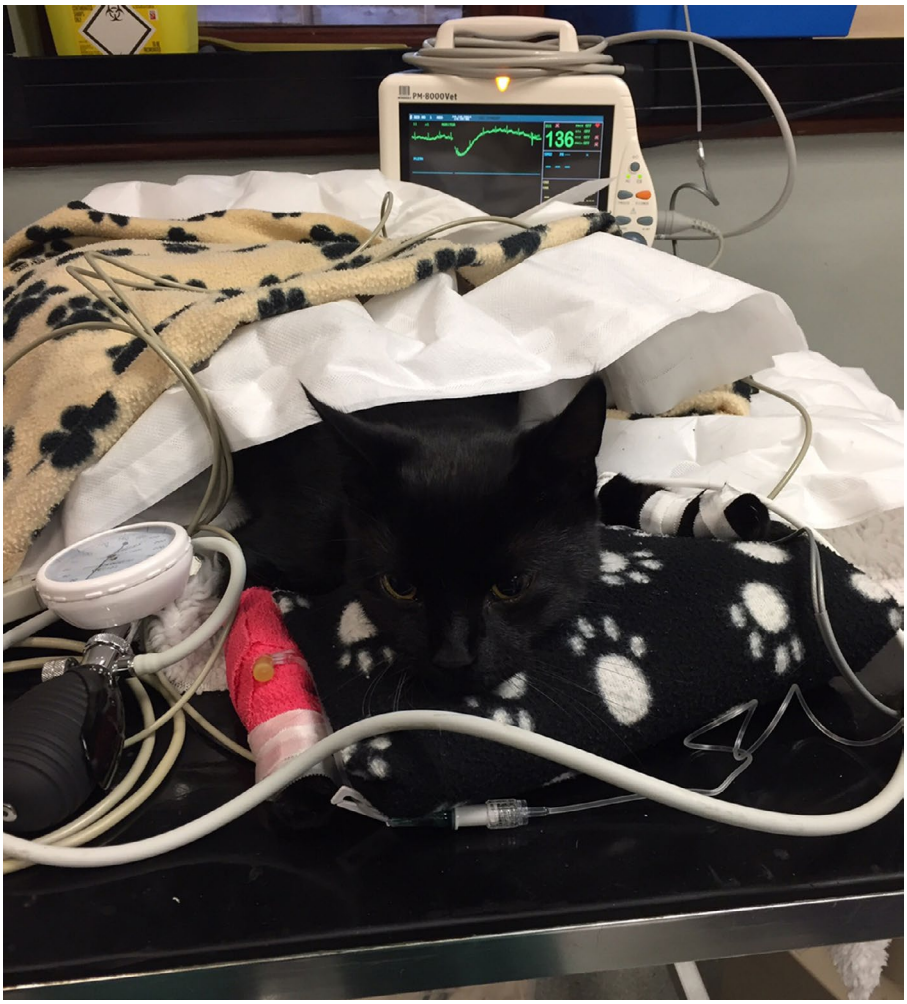

Figure 4. Cat being treated for ethylene glycol toxicity

2. Anticoagulants are added to the blood and uremic toxins are removed and electrolytes are normalised.
3. The blood is returned to the patient.

Box 3. Intermittent haemodialysis

Intermittent haemodialysis (IHD) is a therapeutic procedure by which blood is removed from the patient and run through an artificial kidney called a dialyser. Diffusion occurs across a semi-permeable membrane in the dialyser which removes uremic toxins. Blood circulates in a loop for the length of the dialysis treatment (usually 4–5 h) (Poeppel & Langston, 2012).

Case study

Loki, 1 year old, male neutered domestic short-haired outdoor cat was presented with a 24 h history of progressive lethargy. He had also developed hind limb ataxia 6 h prior to presentation. The owner could not confirm if he had passed urine recently. While the owner had not seen the cat lapping antifreeze, they had lost other cats due to suspected EG poisoning and the referring veterinarian reported several other EG poisoning cases in the locality recently.

On presentation, the patient was in a stuporous mental status and given his critical condition, he was admitted after taking a brief history from the owner. During transportation to the veterinary hospital, the cat was reported to have had one generalised tonic–clonic seizure that had resolved spontaneously before arrival.

An intravenous catheter was already in place, which was flushed to confirm patency and re-bandaged. A blood sample was taken for in-house blood gas and electrolyte analysis, haematology and biochemistry.

The blood gas analysis revealed a markedly decreased pH (7.089, reference range: 7.350–7.450) and bicarbonate (9.6 mmol/l, reference range: 17–24 mmol/l) compatible with severe metabolic acidosis. Electrolyte analysis identified severe hypocalcaemia (ionised calcium: 0.73 mmol/l, reference range 1.10–1.40), which was likely the cause of the seizure witnessed by the owners. The haematology was unremarkable, but the serum biochemistry identified azotaemia (urea: 22.6 mmol/l, reference range: 5.0–10.8 mmol/l; and creatinine: 197 µmol/l, reference range: 60–180 µmol/l. Urinalysis revealed a diluted urine (USG: 1020) and calcium oxalate crystals were seen in the urine sediment. In light of history, clinical signs and the results of the blood and urine tests, acute renal failure due to EG intoxication was the most likely diagnosis. Given that the patient was already in acute renal failure his prognosis was now regarded as guarded to poor (**Figure 4**).

The patient was started on intravenous fluid therapy (Lactated Ringer's solution) at 1.5× maintenance (12 ml/h). A 1 ml/kg bolus of medical grade 95% ethanol was given very slowly IV. In light of the hypocalcaemia a 1 ml/kg bolus of calcium gluconate was given slowly IV (over 10–15 min) while monitoring the heart rate continuously with an ECG. Upon calcium gluconate administration bradycardia ensued and the bolus was stopped. The calcium gluconate infusion was re-started at a slower rate once the patient's heart rate was normal again.

The patient's vitals including heart rate, pulse rate and quality, respiratory rate, capillary refill time and mucous membrane colour and mentation were monitored constantly and recorded every 5 min. Non-invasive oscillometric blood pressure measurement and electrocardiogram where also used to monitor the patient's blood pressure and heart rate and rhythm. The patient's eyes were lubricated every 4 h.

The patient was hypothermic and therefore a Bair Hugger™ was used to warm him.

After the initial calcium gluconate bolus, the mentation of the patient was noted to have improved – he was now lifting his head and described as obtunded. Electrolytes were measured again and the ionised calcium was found to have improved but still below the reference range (0.99 mmol/L). Hence, another bolus of calcium gluconate was repeated. After this the patient was sitting up looking around so was transferred back to his own kennel as one to one nursing was no longer deemed appropriate as the CNS and respiratory depression that resulted from the Ethanol infusion had resolved.

Four hours after hospitalisation when the patient was receiving his second dose of Ethanol he became acutely comatose and underwent respiratory arrest. The owners were called and due to the very poor prognosis they elected Euthanasia.

Sadly, Loki's sister was also presented with EG toxicity on the same day, was treated with ethanol and calcium gluconate but failed to survive. Haemodialysis was discussed with the owner but as prognosis was poor for both cats and funds were unavailable it was declined.

Conclusion

Nursing patients with either suspected or confirmed ethylene glycol toxicity can be challenging, especially as there is such a low minimum lethal dose, high mortality rates and very poor prognosis.

Client education is of paramount importance; making the general public aware of the common signs of antifreeze poisoning and how to prevent it is the only way to reduce the number of patients who are presented.

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Multiple Choice Questions

1. What is the minimum lethal dose of EG for a dog?

(a) 6.6 ml/kg
(b) 1.4 ml/kg
(c) 2.6 ml/kg
(d) 0.5 ml/ kg

2. EG is metabolised by the liver into what?

(a) Glycogen
(b) Glucose
(c) Oxalic Acid
(d) Glycolyic Acid

3. Where in the body does Oxalic acid bind?

(a) Aorta
(b) Renal Tubules
(c) Urethra
(d) Bladder

4. What shape are the urinary crystals associated with this poisoning?

(a) Cuboid
(b) Round
(c) Diamond
(d) Coffin

5. The term 'Anuric' indicates?

(a) The patient is urinating excessively
(b) The patient is unconscious
(c) The patient is not producing urine
(d) The patient is struggling to urinate

6. What, per Willey et al. 2016, should be administered to cats to induce vomiting?

(a) Xylazine
(b) Dexmedetomidine
(c) Alpha-2 Agonist
(d) Any of the above

7. What is referred to when the abbreviation CNS is used?

(a) Central Nervous System
(b) Central Neurons System
(c) Cat Nephron System
(d) Cardio-Neurology Syndrome

8. What antidote can cause respiratory or CNS depression?

(a) Tequila
(b) Charcoal
(c) Lactated Ringers
(d) Vodka

9. Signs of Hypocalcaemia can include

(a) Seizures
(b) Ataxia
(c) Arrhythmias
(d) All the above

10. Azotaemia is elevated levels of?

(a) Urea and Glucose
(b) Urea and Potassium
(c) Urea and Creatinine
(d) Potassium and creatinine

For the answers to the MCQs, please go to: http://www.bvna.org.uk/publications/veterinary-nursing-journal