REVIEW

Common questions in veterinary toxicology

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Toxicology is a vast subject. Animals are exposed to numerous drugs, household products, plants, chemicals, pesticides and venomous animals. In addition to the individual toxicity of the various potential poisons, there is also the question of individual response and, more importantly, of species differences in toxicity. This review serves to address some of the common questions asked when dealing with animals with possible poisoning, providing evidence where available. The role of emetics, activated charcoal and lipid infusion in the management of poisoning in animals, the toxic dose of chocolate, grapes and dried fruit in dogs, the use of antidotes in paracetamol poisoning, timing of antidotal therapy in ethylene glycol toxicosis and whether lilies are toxic to dogs are discussed.

Journal of Small Animal Practice (2015) **56**, 298–306
DOI: 10.1111/jsap.12343

Accepted: 5 January 2015; Published online: 27 February 2015

INTRODUCTION

Toxicology is a vast subject. Animals are exposed to numerous drugs, household products, plants, chemicals, pesticides and venomous animals. There is also the question of species differences in toxicity. To facilitate best treatment it is important to address some of the common questions asked when dealing with animals with possible poisoning, providing evidence where available.

SHOULD WE ROUTINELY MAKE DOGS SICK?

Routine, as in "performed as part of a regular procedure rather than for a special reason" is probably not a good way of applying any intervention; however the induction of emesis is widely accepted as routine in the management of poisoning in animals. Where is the evidence supporting its use?

The efficacy of any method of gastric decontamination declines the longer the time between ingestion and emesis. In one experimental study, dogs were given 5 g of barium sulphate followed by apomorphine at 0, 30 and 60 minutes after administration; this returned 3.9 g (78%), 3.2 g (64%) and 1.27 g (25%) of barium, respectively (Abdallah & Tye 1967). In a similar study, dogs given 1 g of barium sulphate returned 54–87% after administration of apomorphine 20 minutes later (Corby *et al.* 1967). The clinical significance of this is unclear as it does not reflect the typical clinical situation, where animals present many minutes or even hours after ingestion. There is little evidence that emesis empties the stomach completely; this may occasionally occur and certainly there are anecdotal reports of this. In a review of 147 dogs given apomorphine or hydrogen peroxide as an emetic, vomiting occurred in 94% and 90% of dogs, respectively. The mean recovery of ingested material in this study was estimated (by visual inspection of the vomitus and the amount known to have been ingested) as 48% for hydrogen peroxide and 52% for apomorphine (Khan *et al.* 2012). Generally the quantity returned is in the range of 40–60% of the stomach contents (Beasley 1999).

Attempting to empty the stomach is usually only considered worthwhile if ingestion is recent (within 1 to 2 hours), although there is limited (perhaps, no) evidence for this restriction. After this time the ingested material may have been absorbed or passed beyond the stomach and so will not be retrieved with vomiting. However, there are some substances that can remain in the stomach for longer (e.g. raisins and sultanas; whole grapes and swollen raisins have been recovered from dogs even after they have remained in the stomach overnight, however the clinical significance of their prolonged presence in the stomach or delayed removal is unknown [Eubig *et al.* 2005]).

The physical form (e.g. tablet, liquid, slow release formulation) and chemical nature of the substance ingested will also influence the time that material remains available in the stomach (Howland 2006). Nicotine, for example, is a weak base so absorption in the stomach is low because of the low pH (Ivey & Triggs 1978). The presence of food in the stomach may also delay, enhance or prolong absorption (Howland 2006). In addition some substances (e.g. some antihistamines [Chen & Ensor 1950], and phenothiazines [Wyant 1962]) have an anti-emetic effect and so emetics may be ineffective in these cases.

There are a number of contraindications to the use of emetics (Lee 2013), depending on the clinical condition of the animal

Table 1. Contraindications for induction of emesis in animals with poisoning

Emesis should not be induced:

- If the animal
  - has already vomited,
  - is very drowsy or unconscious,
  - is exhibiting seizure activity,
  - has reduced cough reflex,
  - has an underlying condition which predisposed them to aspiration (e.g. megaoesophagus, laryngeal paralysis).
- If the substance ingested
  - is likely to cause rapid onset of drowsiness or seizures,
  - contains paraffin, petroleum products or other oily or volatile organic products which could be aspirated into the lungs,
  - contains detergent compounds, which could be aspirated into the lungs,
  - is a strong acid or alkali, which could cause further damage to the oesophagus if regurgitated.

and the substance ingested (Table 1). There is probably little benefit in inducing emesis in an animal that has already vomited (assuming the animal is not simply retching and that gastric material has been returned); the focus of treatment in these cases should be on the management of clinical signs.

At one time, emetics were used routinely in the management of poisoning in human medicine, but they are now rarely used. The American Academy of Clinical Toxicology (AACT) and European Association of Poison Centres and Clinical Toxicologists (EAPCCT) position statement on the use of syrup of ipecacuanha (ipecac) as an emetic in human poisoning concluded that there is limited good quality data available and that there remains no convincing evidence from clinical studies that ipecac improves the outcome of poisoned patients (Höjer *et al.* 2013). This is also the case in veterinary medicine where although emetics produce vomiting, to the authors' knowledge there is no evidence that vomiting improves the clinical outcome in poisoned animals. In an experimental study in dogs given oral carprofen, activated charcoal alone was as effective as emesis and activated charcoal in terms of time to maximum blood concentrations, maximum concentration, area under the curve and elimination half-life (Schildt *et al.* 2009).

The methods used for induction of emesis are relatively safe and efficacious (that is, they induce vomiting) and it seems logical that removing the contents of the stomach may be beneficial in the management of poisoning, but data supporting or refuting the effectiveness of emesis in animals (other than humans – and here it is negative) is lacking. This means that, for now, pressure from owners, the wish to do something that appears logical, and the pressure of accepted practice means emesis is often used in the management of poisoning in companion animals. Therefore, induction of emesis must be justified in each case, should not be routine and should not be performed in cases where a non-toxic dose of a substance has been ingested.

AN ANIMAL HAS INGESTED A POISON, SHOULD I GIVE CHARCOAL?

Activated charcoal is an adsorbent commonly used in the management of both human and veterinary poisoning. Activated charcoal is a finely powdered material that has been treated to give it a large surface area (~1000 m^2/g), which is capable of binding a variety of drugs and chemicals; this relies mainly on weak intermolecular forces and generally non-polar materials are not well bound. The charcoal is administered orally and is not systemically absorbed or metabolised but passes through the gut reducing or preventing systemic toxicity of the ingested substance. Given as a single dose or in repeated doses, activated charcoal can be given alone as the sole method of gut decontamination, but may also be given after emesis or gastric lavage. Timing of administration is important, as efficacy declines the longer the period between ingestion and administration (AACT/EAPCCT 2005).

The use of activated charcoal in a particular case will depend on the substance ingested. A single dose is most useful when the substance ingested is still in the stomach and in most cases that is all that is required. For a single dose of activated charcoal to be effective in reducing absorption, it must come in direct contact with the ingested substance (AACT/EAPCCT 2005) and therefore must be given as soon as possible after ingestion. Repeat dose administration of activated charcoal is thought to act by interrupting enterohepatic recycling (such as theobromine in chocolate) and/or promoting drug exsorption from the systemic circulation into the gut lumen (AACT/EAPCCT 1999). Repeat doses may be useful, in theory at least, for drugs formulated as sustained or modified release.

The binding of activated charcoal has not been tested against all (or even many) drugs and chemicals, but is known not to significantly adsorb a number of substances such as acids and alkalis, alcohols and glycols (ethylene glycol), metals (e.g. iron, lead), oils and petroleum distillates (e.g. white spirit) and detergents.

Activated charcoal is generally well tolerated but it will stain faeces black and if given to a sedated animal without airway protection can result in aspiration into the lungs with subsequent pneumonitis. It will also make endoscopic evaluation difficult. The use or timing of activated charcoal administration needs to be considered when oral treatments are to be used, as the charcoal may also absorb these and reduce their efficacy. Although there is no evidence to support this, it is reasonable to allow a period of at least 2 hours between administration of charcoal and oral medication. An observational study in humans with paracetamol overdose found that activated charcoal before oral acetylcysteine administration did not significantly interfere with the efficacy of the antidote (Spiller *et al.* 1994).

Administration of activated charcoal may be difficult (and very messy). Ideally it should be given alone as the adsorptive capacity may be reduced if mixed with other substances such as food. Food is commonly added to activated charcoal to improve palatability; there is only one study examining the implication of this in veterinary medicine. The *in vitro* study evaluated the effect of dog food on the adsorptive capacity of activated charcoal using paracetamol as a marker. A statistically significant reduction in the adsorptive capacity of activated charcoal was demonstrated with increasing amounts of dog food. However, all measurements of paracetamol represented a reduction in concentration of more than 98%. It was concluded that the addition of dog food to

activated charcoal does reduce the total adsorptive capacity, but this is unlikely to be clinically significant in the presence of both the formulation of dog food and the ratio of dog food to charcoal used in this study (Wilson & Humm 2013). This, however, is only one study looking at only one drug.

Activated charcoal can be given to an animal that has ingested a potentially toxic dose of a substance if, (1) the substance is known or thought to be adsorbed by activated charcoal, (2) ingestion was very recent or the substance undergoes enterohepatic circulation or the agent is sustained release, (3) the animal is in a clinical condition where it can tolerate activated charcoal and (4) does not require immediate administration of oral medication.

WHAT IS THE TOXIC DOSE OF CHOCOLATE IN DOGS?

The toxic component of chocolate is theobromine, a methylxanthine, but canine toxicity studies on theobromine are limited. Chocolate also contains caffeine but in a lower concentration than theobromine. In dogs a single oral dose of theobromine of 500 or 1000 mg/kg caused panting, restlessness and muscle tremors 4–5 hours after ingestion and lasted 6–8 hours. No dogs given 200 mg/kg or less died, but one of 4 dogs given 300 mg/kg and one of two given 1000 mg/kg died within 5 hours. One of 8 dogs given 500 mg/kg died during the night (Gans *et al.* 1980).

Data from the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poisons Control Center suggest that toxic effects in dogs occur at theobromine doses of 20 mg/kg, with severe signs at 40–50 mg/kg and seizures at 60 mg/kg (Gwaltney-Brant 2001). Fatal cases have occurred in dogs after ingestion of 80–300 mg/kg (EFSA 2008).

If the toxic dose of theobromine is 20 mg/kg then it is important to understand the various types of chocolate. This is defined by the quantity of cocoa solids present (Table 2). Chocolate is made from the fermented, dried then roasted beans of *Theobroma cacao*. These are ground to cocoa mass which is liquefied to produce chocolate liquor which can then be processed into cocoa solids and cocoa butter. The percentage of cocoa solids in a particular chocolate cannot be converted into the quantity of theobromine. It only describes the type of chocolate (dark, milk or white). Numerous sources list the range of theobromine content in various chocolate sources. Table 2 also provides the approximate dose of product equivalent to 20 mg of theobromine.

There may be a genetic component to individual susceptibility to chocolate toxicity. Dogs with CYP1A2 1117C>T polymorphism may be more at risk of toxicity due to reduced metabolism. Dogs with this polymorphism have complete loss of enzyme function and have been shown to have higher plasma AUC values and longer half-lives of theobromine compared to CYP1A2 wild-type dogs. Lower concentrations of metabolites are also found in the urine of deficient dogs (Collica 2012). This polymorphism is widespread across different dog breeds (Aretz & Geyer 2011).

WHAT IS THE TOXIC DOSE OF RAISINS, SULTANAS OR GRAPES IN DOGS?

Grapes, grape skins, marc (the residue of grapes after pressing) and their dried products (raisins, sultanas and currants) can cause renal failure in dogs. Cases have been reported from the United Kingdom (Penny *et al.* 2003, Sutton *et al.* 2009), America (Gwaltney-Brant *et al.* 2001, Mazzaferro *et al.* 2004, Eubig *et al.* 2005, Morrow *et al.* 2005, Stanley & Langston 2008), Australia (Lovell & Harvey 2006) and Korea (Oh *et al.* 2008, Yoon *et al.* 2011). The fruits can be ingested raw or cooked in fruit cakes (including Christmas cake) and other baked goods.

The toxic mechanism that results in renal toxicity remains unknown but the lack of dose response may reflect a component of grapes or their products that is present in varying quantities or an extrinsic compound that is not always present in or on the grapes (Eubig *et al.* 2005). Hypotheses include canine tannin intolerance (Singleton 2001), contamination of fruits with mycotoxins, pesticides or heavy metals (Gwaltney-Brant *et al.* 2001), idiosyncratic reactions due to enzymatic differences (Mazzaferro *et al.* 2004) or ingestion of excess vitamin D (Gwaltney-Brant *et al.* 2001).

Table 2. Approximate theobromine content of chocolate products

Type of chocolate product	Definition	Theobromine§ content per g (median*)	Approximate dose of product equivalent to 20 mg of theobromine
Milk chocolate	UK and Ireland ("family milk chocolate" in rest of Europe): minimum 20% cocoa solids. Rest of Europe: minimum 25% cocoa solids.	1.0–2.1 mg (median 1.4)	9.5–20 g (14.3 g)
Dark (or plain) chocolate (Semi-sweet, bitter or extra dark chocolate in America).	European law does not recognise the term "dark" or "plain" and it is just known as "chocolate". Minimum 35% cocoa solids (can be much higher), at least 18% of which should be cocoa butter.	4.4–8.8 mg (median 5.3)	2.3–4.5 g (3.8 g)
Cocoa beans	Dried, fermented seeds of Theobroma cacao.	10–54 mg	0.5–2.7 g
Cocoa powder	Non-fat part of the cacao bean (after the cocoa butter has been removed) ground into a powder.	4.6–38 mg (median 26)	0.2–1.9 g (0.78 g)
White chocolate	Primarily cocoa butter, sugar and milk solids (no cocoa solids).	Insignificant	Risk of theobromine toxicity minimal.

§The amount of theobromine in products will vary due to natural differences in cocoa beans and the formulation of the products
*The median was determined using the maximum concentration measured (where a range was given) in all the relevant sources
Sources: de Vries *et al.* 1981, Craig & Nguyen 1984, Fincke 1989, Matissek 1997, Risner 2008, Sjdenovic *et al.* 2008, Meng *et al.* 2009

The fatal dose of grapes or grape products has not been established and case reviews have shown no relationship between the dose ingested in dogs that died and those that survived (Eubig *et al.* 2005). The lowest doses of grapes reported to result in renal failure is 4 or 5 grapes in one dog and 2.8 g/kg in another (Eubig *et al.* 2005). For raisins the lowest dose to cause renal failure is 3 g/kg (Morrow *et al.* 2005). In a review of 49 Veterinary Poisons Information Service (VPIS) cases a higher proportion of dogs that ingested dried fruit (73.5%) developed clinical signs compared to those that ingested grapes (26.5%). Of the 17 fatal cases 12 had ingested dried fruits and 5 had ingested grapes (Sutton *et al.* 2009).

Some dogs appear to be capable of eating grapes and grape products without developing adverse effects (Sutton *et al.* 2009). However, in view of the lack of a known dose response, reported cases of renal failure from a small quantity (Table 3), the unknown mechanism and lack of knowledge about other issues such as individual risk factors, treatment is recommended following ingestion of any quantity of grapes or grape products in dogs. It is also worth noting that time to treatment may also play a significant role in outcome. In 49 VPIS cases reviewed the mean time to contact with VPIS (and therefore recommendation for treatment) in asymptomatic dogs was 7 hours compared to 23 hours for symptomatic cases and 59 hours in fatal cases (Sutton *et al.* 2009).

WHAT IS THE APPROPRIATE ANTIDOTE FOR PARACETAMOL POISONING?

Paracetamol (acetaminophen) toxicity is one of the commonest causes of drug-induced poisoning in both human and veterinary medicine, in part due to its ready availability. Paracetamol is metabolised by the liver by glucuronidation, sulphonation and oxidation pathways. All detoxification pathways produce non-toxic metabolites which are excreted in the urine and/or bile. The oxidation pathway, however, also results in formation of a highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI). This conjugates with glutathione which limits its toxic effects but once glutathione stores are exhausted, NAPQI binds to macromolecules and proteins causing liver tissue necrosis (Hodgman & Garrard 2012).

In addition glutathione is involved in the processing of methaemoglobin to haemoglobin, and once it is depleted methaemoglobin concentrations increase. Haematological toxicity after paracetamol poisoning is rarely reported in humans (Kanji *et al.* 2013), but it can be severe in paracetamol-poisoned cats. Alternative paracetamol metabolic pathways result in Heinz body formation, denaturation of erythrocyte membranes and additional methaemoglobin formation further promoting tissue hypoxia (Jones *et al.* 1992). Factors influencing paracetamol sensitivity include the quantity ingested, malnourished state, interspecies differences in glutathione concentrations and interspecies limitations in capacity and saturation of glucuronidation and/or sulphonation pathways. For example, cats are much more susceptible to paracetamol toxicity than dogs due to the limited capacity of their glucuronidation pathway and saturation of their sulphate conjugation pathway (Savides *et al.* 1984).

The aim of antidotal therapy in the management of paracetamol toxicity is to replace glutathione stores, increase the productivity of the other two pathways and manage the haematological signs. Some antidotes may also conjugate the NAPQI or limit paracetamol metabolism that occurs through the action of CYP P450 (such as cimetidine). However, experimental studies in rodents have shown that cimetidine is less efficacious then acetylcysteine (Jackson 1982), although it appears to enhance

Table 3. Doses of grape and grape products causing renal failure in dogs

Product	Dose	Time to presentation or onset of signs	Outcome	Reference
Currants	7.8 g/kg	4 days	Recovery	Stanley and Langston 2008
Raisins	20.6 g/kg	12 hours (onset), 4 days (presentation)	Recovery	Mazzaferro *et al.* 2004
Raisins	15.67 g/kg	8 hours (onset), 24 hours (presentation)	Died	Mazzaferro *et al.* 2004
Raisins	3–30 g/kg, median 21 g/kg (6 dogs)	Not stated	Died or euthanised	Morrow *et al.* 2005
Raisins	4.8 g/kg	24 hours (presentation and 4 days for re-presentation)	Died	Mazzaferro *et al.* 2004
Grapes (fresh, fermented or crushed) or raisins	11.5–31 g/kg (10 dogs)	Not stated	Five recovered, two died, three euthanised	Gwaltney-Brant *et al.* 2001
Grapes	4–5 grapes in an 8.2 kg Dachshund	1 day (presentation)	Recovery	Mazzaferro *et al.* 2004
Grapes	21 and 30 g/kg (2 dogs)	Not stated	Died or euthanised	Morrow *et al.* 2005
Grape skins	18.75 g/kg	12 hours (onset)	Recovery	Oh *et al.* 2008
Grapes	19.6, 30.8, 50.4 and 148.4 g/kg	Not specified for individual cases; 81% of dogs developed signs within 24 hours	Not specified for individual cases; of 43 dogs 5 died (12%), 15 were euthanised (35%) and 23 survived (53%)	Eubig *et al.* 2005
Raisin or sultanas	2.8 to 36.4 g/kg in 24 dogs			
Grapes	10–12 grapes			

Note that sultanas are more popular in Europe and are the dried fruit of a white grape. The term raisin applies to the dried fruit of a dark grape and currants are the dried fruit of the small Black Corinth grape

the hepatotoprotective effect of acetylcysteine (Al-Mustafa *et al.* 1997). Cimetidine is generally not used in the management of paracetamol poisoning in humans, and to the authors' knowledge there are no clinical studies in cats or dogs examining the effect of cimetidine in acute paracetamol poisoning.

Both methionine and acetylcysteine provide glutathione precursors, and by restoring glutathione concentrations they have a twofold mechanism in alleviating toxicity: (1) by continuing metabolism of paracetamol via the oxidation pathway which results in non-toxic metabolites and (2) replacing glutathione for normal metabolic functions thereby correcting haematological changes. Furthermore, they also increase the sulphonation pathway by forming sulphate when metabolised. Unlike methionine, however, acetylcysteine conjugates NAPQI which is then excreted via the kidneys; however, this has a minor role and excretion (in humans) is slow (Prescott 1983, Ferner *et al.* 2011).

Other antidotes act to increase alternative pathways and thereby promote metabolism of paracetamol via non-toxic pathways. S-Adenosyl methionine (SAMe) is a precursor to intracellular oxidant molecules including glutathione. It is cytoprotective and increases sulphonation and glucuronidation pathways. In a clinical case SAMe appeared to prevent paracetamol-induced hepatotoxicity in a dog that presented 48 hours after ingestion (Wallace *et al.* 2002) and in an experimental study in cats it protected against haematological effects (Webb *et al.* 2003). Data on the use of SAMe in clinical cases of paracetamol poisoning, however, are limited and insufficient to recommend it as the sole therapy.

Other interventions are not antidotes in themselves and will not prevent progression of liver necrosis. They will, however, alleviate haematological abnormalities associated with paracetamol toxicity such as methaemoglobinaemia. Both ascorbic acid and methylene blue (methylthioninium chloride) may be used. Although methylene blue can itself cause methaemoglobinaemia and haemolytic anaemia, particularly in cats, it is safe to use at correct doses (Rumbeiha & Oehme 1992). Ascorbic acid has reductant properties (although the reaction occurs slowly) and can convert methaemoglobin to haemoglobin; it also scavenges NAPQI before it binds to proteins (Lake *et al.* 1981). It is usually used in combination with the other antidotes.

To the authors' knowledge there are no clinical trials on the use of antidotes in the management of paracetamol poisoning in cats and dogs. Acetylcysteine is the recommended antidote for paracetamol toxicity and the standard therapy in both human and veterinary medicine. It is recommended even in cases with late presentation, although efficacy declines with increased time post-ingestion. Methionine is not currently used in the management of paracetamol poisoning in humans in many countries and is less readily available. It can be used if there is a delay in sourcing acetylcysteine and can be used in conjunction with acetylcysteine. A systematic review of paracetamol treatments in humans found that methionine and acetylcysteine are similar in efficacy, although acetylcysteine has the advantage of being available in both intravenous and oral preparations, unlike methionine which is only available as oral tablets (Brok *et al.* 2006). It has been suggested that SAMe may be more efficacious than acetylcysteine and may also prevent haematological damage in paracetamol poisoning; however, this evidence is limited to a few reports (Walker *et al.* 2002, Webb *et al.* 2003) and the comparative efficacy data is based on rodents when administered before paracetamol and 1 hour post-exposure (Terneus *et al.* 2007, Terneus *et al.* 2008). This is not representative of the situation in clinical practice where there is often delayed presentation or chronic administration. Therefore, whilst SAMe cannot currently be recommended as the sole antidote, it can be given with acetylcysteine or whilst acetylcysteine is sourced (if not readily available).

The most appropriate antidote for paracetamol poisoning is acetylcysteine; however, SAMe and ascorbic acid are recommended for use with acetylcysteine alongside any other supportive therapies. Methionine could be used if acetylcysteine was not immediately available.

WITHIN WHAT TIME PERIOD IS ANTIDOTAL THERAPY USEFUL FOR ETHYLENE GLYCOL POISONING?

The major toxic agent in ethylene glycol poisoning is not the parent compound but the metabolites produced by the action of alcohol dehydrogenase. This enzyme oxidises ethylene glycol to glycoaldehyde (Coen & Weiss 1966). This is then metabolised to glycolic acid which appears to be the principle cause of the acidosis observed with ethylene glycol toxicity (Jacobsen *et al.* 1984). Further metabolites of glycolic acid are glyoxylic acid and then oxalate (Winek *et al.* 1978); the latter causes renal damage and hypocalcaemia by binding to calcium to form calcium oxalate (crystals of which may be present in urine).

The aim of antidotal therapy in the management of ethylene glycol toxicosis is to prevent formation of these toxic metabolites. 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.

Ethylene glycol is rapidly absorbed from the gastrointestinal tract. In cats peak plasma concentrations occur about 1 hour after ingestion and urine concentrations peak at about 3 hours (Connally *et al.* 2010). In dogs the peak plasma concentration occurs at 2–3 hours (Grauer *et al.* 1984, Grauer *et al.* 1987, Hewett *et al.* 1989) with an elimination half-life of 3.5 hours (Hewlett *et al.* 1989). The urine ethylene glycol concentration in dogs peaks at 6 hours (Grauer *et al.* 1984).

After ingestion of ethylene glycol the sooner antidotal therapy is started the better the outcome. The lethal dose of ethylene glycol in cats is commonly reported as 1.5 ml/kg (Milles 1946), but 1 g/kg (approximately 1 ml/kg) was fatal to cats within 48 hours (Gessner *et al.* 1961). In the study by Connally *et al.* (2010) cats only survived lethal doses of ethylene glycol (1.6 or 3.2 ml/kg) if treated with fomepizole or ethanol at or before 3 hours. Of the nine cats treated within this time, seven survived (78%). One developed renal failure but survived and two were euthanased

Table 4. Treatment, outcome and time to death in ethylene glycol-poisoned dogs treated with ethanol or fomepizole

Dose	No of dogs	Treatment and time	Survivors	Fatal	Time to death	Reference
10 ml/kg	3	1 hour; ethanol and sodium bicarbonate	0	3	5, 22 and 312 hours	Sanyer *et al.* 1973
6 ml/kg	4	2 hours; ethanol and sodium bicarbonate	3	1	264 hours	Sanyer *et al.* 1973
8 ml/kg	5	2 hours; ethanol and sodium bicarbonate	3	2	77 and 336 hours	Sanyer *et al.* 1973
8 ml/kg	4	4 hours; ethanol and sodium bicarbonate	0	4	mean survival 27 hours	Sanyer *et al.* 1973
10.6 g/kg	5	5 hours; fomepizole	5	0	Not applicable	Dial *et al.* 1994
6 ml/kg	4	6 hours; ethanol and sodium bicarbonate	2	2	18 and 99 hours	Sanyer *et al.* 1973
10.6 g/kg	6	8 hours; fomepizole	4	2	After 48 hours and 8 weeks	Dial *et al.* 1994
unknown, clinical cases	7	8.5–38 hours; fomepizole	0	7	Not stated	Connally *et al.* 1996

with renal failure. Two cats treated at 4 hours were euthanased with renal failure. In an earlier study, of 9 cats given lethal doses of ethylene glycol (4, 6 or 8 ml/kg) and treated with ethanol at 4 hours, 5 (55.5%) survived compared to only 1 (8%) survivor of 12 cats treated at 8 hours (Penumarthy & Oehme 1975).

These studies therefore suggest that survival is most likely in cats if treatment with ethanol or fomepizole is started within 3–4 hours of ingestion.

The lethal dose of ethylene glycol in dogs is generally quoted as 6–6.6 ml/kg (Sanyer *et al.* 1973, Hewlett *et al.* 1983, Kersting & Nielsen 1966). Experimental studies and clinical cases in dogs (Table 4) suggest survival is most likely in dogs if treatment is commenced within 6–8 hours of ethylene glycol ingestion.

There is no benefit giving ethanol or fomepizole to block metabolism if the ethylene glycol has already been metabolised and these antidotes should not be used in animals with renal failure. 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. Recovery may take 3–5 days if the animal is treated aggressively within a few hours of ingestion (Connally *et al.* 2010) but in most cases, unless the ingestion was witnessed, animals usually present in the final stage of poisoning. Coma or renal failure indicates a poor prognosis in animals with ethylene glycol toxicosis. In 25 cases of ethylene glycol ingestion in cats the mortality rate was 96%, compared to 70.4% in 35 canine cases (Rowland 1987). Of 26 cats and 24 dogs with ethylene glycol poisoning only 6 animals (12%) survived and half of the survivors were admitted within 12 hours (Thrall *et al.* 1984). In 65 VPIS cases of cats with renal signs after ethylene glycol ingestion 2 (3%) recovered, 12 (19%) died and 51 (79%) were euthanised. The overall death rate in 65 cats with renal failure from suspected ethylene glycol ingestion was 97% (VPIS unpublished data). In a review of 37 canine cases of confirmed ethylene glycol ingestion treated with fomepizole, none of the dogs admitted with azotaemia survived. Seventeen of 19 dogs that did not have azotaemia on admission recovered (Connally *et al.* 1996). Animals can survive a fatal dose of ethylene glycol but only if antidotal treatment is started within a few hours of ingestion.

ARE LILIES TOXIC TO DOGS?

Lilies, that is, species of *Lilium* (true lily) and *Hemerocalis* (day lily), cause renal failure in cats. Cats are the only species reported to develop renal damage from lilies and all parts of the plant are nephrotoxic to cats. The toxic principle(s) and mechanism are unknown (Volmer 2002, Tefft 2004), but renal failure is due to necrosis of renal tubular epithelial cells. In an experimental study in cats the toxic component was found to be water-soluble, and the aqueous flower extract was more toxic than the aqueous leaf extract (Rumbeiha *et al.* 2004).

In a review of National Animal Poison Control Center (NAPCC) data, cats were the only species to develop renal failure with *Lilium longiflorum*. Dogs, even when a large quantity had been ingested, developed only gastrointestinal signs with no renal impairment (Hall 2007).

Of 54 VPIS cases of dogs eating *Lilium* or *Hemerocallis* species alone, 28 dogs (51%) remained asymptomatic. Of the remaining 26 dogs, vomiting was the most common sign (23 dogs). Six dogs had diarrhoea and two of these had bloody stools. No clinical or laboratory signs of renal toxicity were reported in any dog (VPIS unpublished data). Gastrointestinal signs can occur in dogs that ingest *Lilium* or *Hemerocallis* lilies but nephrotoxicity is not expected.

It is important to note that many plants have lily in their name, such as lily of the valley (*Convallaria majalis*), peace lily (*Spathiphyllum* species) and calla or arum lily (*Zantedeschia aethiopica*). These plants are not discussed here and may have different toxic effects.

WHAT IS LIPID INFUSION? CAN I USE IT IN MY PATIENT?

Infusion of lipids is a relatively new treatment used in the management of poisoning in humans and animals. Off-label use of intravenous lipids (Intralipid® 20%, Fresenius Kabi, is most commonly used) have a place in the management of compounds that are lipophilic or cardiotoxic. Most veterinary cases reported involve permethrin (Brückner & Schwedes 2012, Haworth & Smart 2012, Kuo & Odunayo 2013, DeGroot 2014) or macrocyclic lactones such as moxidectin and ivermectin (Crandall & Weinberg 2009, Bates *et al.* 2013, Kidwell *et al.* 2014), but lipid infusion has also been successful in the treatment of toxicity with other compounds such as lidocaine (O'Brien *et al.* 2010), diltiazem (Maton *et al.* 2013), baclofen (Bates *et al.* 2013, Edwards *et al.* 2014) and ibuprofen (Bolfer *et al.* 2014); the list continues to grow.

In most cases the suitability of a compound for treatment with intravenous lipid therapy is determined by two factors: its lipophilicity and half-life. Lipophilicity is described by its partition coefficient (log *P*), where lipid soluble compounds have a high log *P* (e.g. permethrin has a log *P* of 6.5, compared to metaldehyde that has a log *P* of 0.12). Lipid infusion is only suitable for lipophilic compounds with short to moderate half-lives; it is not suitable for lipophilic compounds with long-lives such as vitamin D compounds (e.g. calciferol, calcipotriol) and anticoagulant rodenticides (e.g. brodifacoum, bromadiolone).

The mechanism of action of lipid infusion is not fully understood and there are two main theories, a "lipid sink" mechanism and a metabolic effect. It is thought that the lipid phase formed by intravenous lipid emulsion in the blood acts to sequester lipophilic drugs, making them unavailable to act on their target receptors (Weinberg 2006). In drugs causing cardiotoxicity, lipids may reduce toxic effects by providing a source of energy to the myocardial cells (Van de Velde *et al.* 1996).

The risks of lipid infusion in the context of treatment of drug toxicity (rather than as part of parenteral nutrition) are unknown, but it is generally considered safe (Fernandez *et al.* 2011). Pancreatitis (Gwaltney-Brant & Meadows 2012), hyperlipidaemia (Gwaltney-Brant & Meadows 2012, Maton *et al.* 2013) and extravasation with pain and local swelling (Bates *et al.* 2013) have been reported as adverse effects in veterinary cases. Other potential risks include hypersensitivity reactions, fat embolism, thrombophlebitis and microbial contamination of the lipid emulsion from inappropriate handling or use of a non-sterile technique (Fernandez *et al.* 2011).

Administration of lipids in animals receiving therapy with lipophilic drugs such as propofol has been raised as a potential concern; however the use of lipid is expected to reduce the need for such emergency therapy. The potential effect of lipid infusion on concentrations of other therapeutic agents including antidotes should be assessed on an individual case basis.

How do we know lipid infusion works? There are currently no published clinical trials evaluating the efficacy or safety of lipid infusion in acutely poisoned human patients (Jamaty *et al.* 2010), but there are a growing number of case reports and small case series in the veterinary literature. There is also experimental data (e.g. Weinberg *et al.* 2003). The only clinical trial of lipid infusion in the management of poisoning is a randomised controlled trial in permethrin-poisoned cats. Cats given lipid had a lower clinical score (based on the expected progression of clinical signs in permethrin toxicity) earlier compared to controls and it was concluded that lipid was a useful therapy in the treatment of permethrin toxicity in cats (Peacock *et al.* 2013). Much, however, remains unknown. The mechanism is not fully understood and the optimal dosage regimen or lipid formulation has not been established. In addition lipid has been ineffective in some cases (e.g. Wright *et al.* 2011) and reasons for this have not been fully elucidated.

Intravenous infusion of lipids can lead to dramatic improvement in animals with poisoning, reduce hospitalisation time and save lives. This is a simple, easy to administer and cheap treatment that is becoming a promising adjunct to conventional treatments in the management of toxicity caused by lipophilic and cardiotoxic compounds. It may be considered in any patient showing clinical signs of serious toxicity after exposure to a lipophilic compound. Intravenous lipid emulsion therapy does not replace conventional antidotes or supportive care, and further research into its efficacy and safety is needed.

Conclusions

Although we have covered some subjects that may be of interest, it is likely that the next poisoning case is not addressed. If it involves an unfamiliar substance it is strongly advised specialist advice from a poisons information centre is sought. Even if no animal data are available these services can give general advice on potential risks and treatment options.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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