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Common Poisonings in Small Animals Mini Series

Session One: General Approach to the Poisoned Patient and Neuromuscular Toxins

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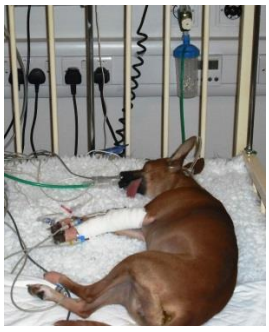

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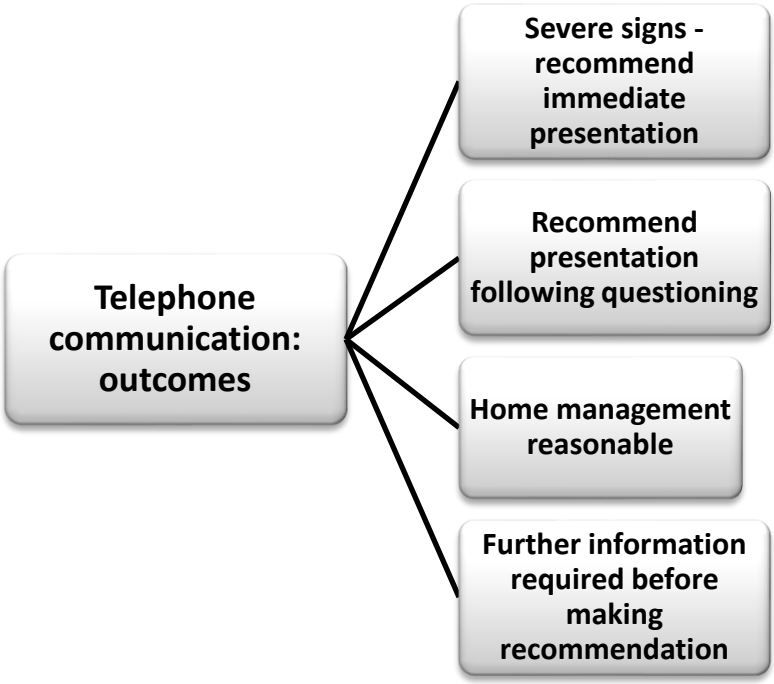
General Approach to the Poisoned Patient

Suspected or witnessed poisoning is a common reason for presentation of small animals to emergency clinics, with dogs being much more commonly affected than cats. These notes present a general approach to the poisoned patient before going on to describe some of the more commonly implicated poisons in greater detail.

Telephone communication



Initial telephone communication is perhaps no more important than in the intoxicated patient. The important questions to ask are summarised below.

Was exposure witnessed or is it suspected? If suspected, based on what evidence? What poison/poisons are involved? Can the owner provide more specific details – quantity, concentration etc.? Where appropriate, does the owner have access to the container? • The owner should be asked to bring this with them if the animal is presented to the practice What is the animal's signalment and estimated body weight? How long ago did exposure occur? By what route did exposure occur? Is the animal showing clinical signs? If so, what are they, when did they start and what is their progression? Is the owner sure that this is the only animal to be affected? Does the animal have any pre-existing medical conditions? Is the animal currently taking any medications?

Nurses are frequently the first members of staff with which owners ringing about suspected or witnessed poisoning will communicate. It is therefore imperative that all nurses are well rehearsed in the questions that are important to ask and advice should be sought from the veterinary surgeon if there is any concern.

On the basis of the information obtained a recommendation should be made as to whether the animal needs to be presented to the practice or may be managed conservatively at home. In some cases, the animal will be exhibiting marked clinical signs and questioning should be kept to a minimum with immediate transport to the practice being the only appropriate recommendation. In other cases, it is necessary to obtain further information before a recommendation can be made.

Further information

The purpose of seeking additional information about the poison in question is to ascertain if possible the severity of exposure that has or may have occurred:

Has potentially toxic exposure occurred?
Has lethal exposure occurred?
What are the expected clinical signs?
Would the animal be expected to have developed clinical signs by now?
If signs are present, are they reported to be early or late signs of intoxication? Is their progression typical?

A number of sources of information are available with respect to veterinary toxicology that includes:

- The Veterinary Poisons Information Service (VPIS) in the United Kingdom
- Toxcall in the United Kingdom
- The ASPCA Animal Poison Control Center in North America
- Pet Poison Helpline in North America
- Books on veterinary toxicology
- The internet: only reliable up-to-date sources should be used (e.g. www.vin.com, www.ivis.org, www.merckvetmanual.com). The internet is also useful for determining ingredients and concentrations in cases where for example only a proprietary product name is available

Some information that may be useful when calculating exposure dosages is:

- 1 standard teaspoon = ~ 5 ml; 1 standard tablespoon = ~ 15 ml
- 1 fluid ounce (oz) = 29.6 ml; 1 ml = 0.034 oz
- 1 lb = 0.454 kg; 1 kg = 2.2 lb
- 1% solution = 10 mg/ml = 1 g/100 ml
- 1 part per million (ppm) = 1 mg/kg for solid substances, 1 mg/l for liquid substances
- *w/w:* an abbreviation for 'by weight'; used to describe the concentration of a substance in a mixture or solution. In strict terms, 8% w/w means that the mass of the substance in question is 8% of the total mass of the solution or mixture. The metric symbol g/g has the same meaning as w/w.

Home management

If the decision is made for the animal to be monitored at home, the owner must be thoroughly briefed both on what signs to observe the animal for and the typical timeframe for their onset and progression. In general, if there is any doubt as to the animal's condition, veterinary examination should be recommended. Owners should be advised on appropriate measures to implement during transportation. For example keeping unconscious animals warm or keeping seizuring animals cool and protected from injury.

Inducing emesis at home:

In some cases in which poison ingestion has occurred within a suitable period of time, it may be appropriate for the owner to induce emesis at home, for example if financial concerns or practical constraints preclude presentation to the practice. In addition, if a considerable delay is anticipated prior to presentation, and the owner has ready access to an appropriate emetic, inducing emesis prior to departure from home may be advisable to minimise further absorption of the poison in transit. The owner must be questioned carefully to ensure that contraindications to inducing emesis do not exist.

CONTRAINDICATIONS TO INDUCING EMESIS include:

Significantly altered mentation: increases the risk of aspiration of vomitus; in particular in depressed animals in whom there may be dysfunction of the gag reflex
Respiratory distress and pre-existing conditions (e.g. laryngeal paralysis) may predispose the animal to aspiration.
Animals that are **already vomiting** clearly do not require emesis to be induced.
Emesis should not be induced following ingestion of a **caustic or corrosive agent** (e.g. acids or alkalis) as it will potentially expose the oropharyngeal and oesophageal mucosa to further injury. Consumption of milk or water should be encouraged (if not contraindicated) to dilute the poison.

Agents for inducing emesis at home [C – cats; D – dogs]

Agent	Dose	Comments
Soda crystals (washing soda)	D, C: 1 crystal	Used most often Place on tongue at back of mouth Emesis usually within 10 minutes Can be repeated NB. Not caustic soda (sodium hydroxide)
Syrup of ipecacuanha (7%)	D: 1-2 ml/kg per os C: 3.3 ml/kg per os	Emesis usually within 30 minutes Can be repeated once Bitter taste therefore poor compliance Available in UK?
Hydrogen peroxide (3%)	D, C: 1-3 ml/kg per os	Emesis usually within 10 minutes Can be repeated once Care to avoid aspiration

It is very important to **make sure that soda crystals (washing soda) are used for emesis, as owners have inadvertently administered caustic soda (sodium hydroxide) instead**. This is very harmful following ingestion causing severe injury to the oropharyngeal and oesophageal mucosa with potentially fatal consequences. It may be increasingly difficult to access washing soda in the form of crystals and powdered equivalents will likely make dosing more challenging.

Table salt is an unreliable emetic and may induce or exacerbate hypernatraemia with potentially severe consequences. Its use as an emetic is not recommended, especially in the home environment where owners may accidentally give excessive quantities. Ad lib access to water is imperative if table salt is used.

General clinical approach

- Perform major body system examination and institute immediate life-saving measures as necessary
- Perform emergency database
- Obtain thorough history at first reasonable opportunity
- Minimise further systemic absorption of poison
- Administer antidote if available
- Promote elimination of any poison already absorbed
- Perform further clinical evaluation as appropriate
- Provide symptomatic, supportive and nursing care as appropriate
- Ensure close monitoring and regular repeat clinical evaluation as appropriate

OR:

R Resuscitation/Stabilisation. Risk Assessment.
S Symptomatic/Supportive care, monitoring, nursing care
I Investigations

D Decontamination
E Enhanced elimination
A Antidotes
D Discharge!

History

In patients presenting with severe clinical signs (e.g. seizures, severe muscle tremors) history-taking should not be prioritised over initial stabilisation, especially as specific antidotes are not available for the majority of poisons to which dogs and cats are exposed. Ultimately treatment is directed at the patient and not the poison.

All the information already described should be obtained at the appropriate time. In some emergency patients, clinical signs and progression are compatible with possible intoxication without an immediately suggestive history. In such cases, the owner must be carefully and thoroughly questioned to establish whether a potential source of poison exists that the owner has not considered.

Historical findings associated with possible poison exposure are:

- Sudden and rapid onset of an illness (especially gastrointestinal, neurological, cardiac dysrhythmias, liver or kidney failure) in a previously healthy animal especially after a period of being unsupervised
- Sudden onset of progressive tremors, muscle twitching or seizures in a previous healthy animal
- Possible exposure to poisons including change of diet, access to new areas or environment
- Access to veterinary or human medications

Initial stabilisation – major body system examination

As for all emergency patients, a major body system (cardiovascular, respiratory, central neurological) examination should be performed and immediate measures taken to correct potentially life-threatening problems. Rectal temperature is also usually measured early as part of the primary survey where abnormalities, hyperthermia in particular, are suspected.

Cardiovascular assessment:

Cardiovascular assessment should focus on assessing systemic perfusion (using heart rate, peripheral pulse rate and quality, mucous membrane colour, capillary refill time) and on the detection of possible dysrhythmias. Numerous toxins (e.g. methylxanthines, illicit drugs) can cause severe life-threatening dysrhythmias (ventricular or supraventricular) that might require immediate recognition and appropriate treatment.

Respiratory assessment:

Respiratory assessment should evaluate respiratory rate, effort and thoracic auscultation. Patients may aspirate during vomiting or seizure activity resulting in aspiration pneumonia. Severe twitching and seizure activity can also cause non-cardiogenic pulmonary oedema. Oxygen supplementation via flow-by or via a mask should always be administered to patients with respiratory distress.

Neurological assessment:

The patient's mentation will influence the decontamination procedure chosen. Patients should also be assessed for muscle tremors, twitching or seizures. Seizure activity and severe muscle tremors should be addressed rapidly.

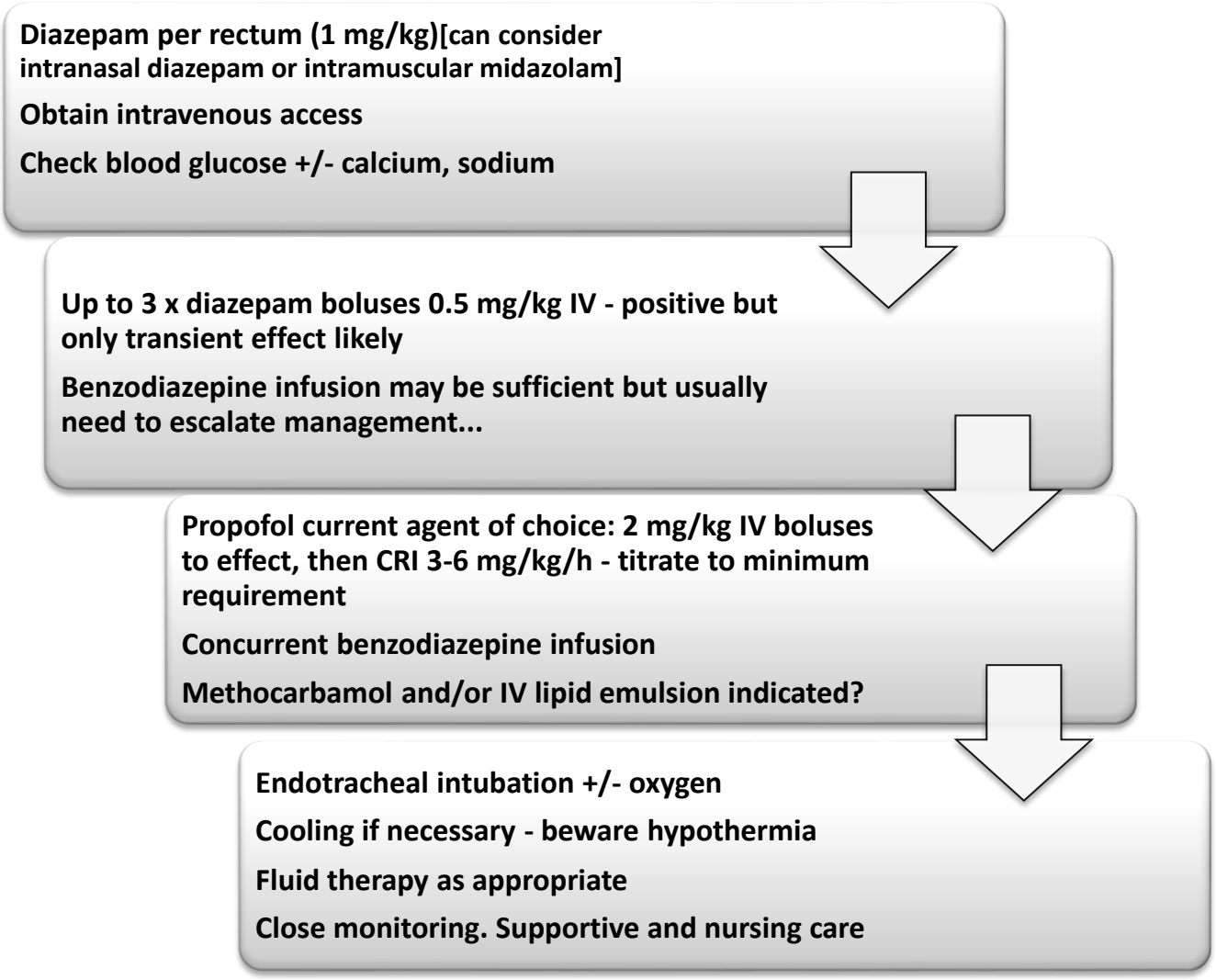
Body temperature:

In appropriate cases, rectal temperature should be measured as early as possible during initial examination as muscle fasciculations and seizure activity can cause hyperthermia. If hyperthermia is present it is important to initiate active cooling. Hypothermia may also occur following bathing or sedation. Close monitoring of rectal temperature for either development and appropriate intervention is therefore required.

Initial stabilisation – treatment of seizures and muscle tremors

A variety of poisons include neurotoxicity amongst their mechanisms of action. Examples include: metaldehyde, pyrethroids; theobromine (chocolate), caffeine, organophosphates, tremorgenic mycotoxins, strychnine. Seizures and/or muscle tremors are common signs of poisoning requiring symptomatic treatment.

Summary of approach to stabilisation of intoxicated patient presenting with seizures and/or severe muscle tremors:



In patients intoxicated with tremorgenic poisons (e.g. metaldehyde, permethrin), it can be difficult to differentiate severe muscle tremors from seizure activity. However if the poison in question is known to be one associated with severe tremors or sufficient clinical suspicion exists, the use of **methocarbamol** (Robaxan©) may be indicated and may avoid the need for anaesthesia. This is a centrally-acting muscle relaxant related to guaiphenesin whose precise mechanism of action remains unclear. The manufacturer's recommended dose in dogs and cats is 44-220 mg/kg IV with a typical upper limit of 330 mg/kg in a 24 hour period; the use of low rate methocarbamol infusion has also been described. However to the author's knowledge an injectable preparation of this agent is not currently available in the United Kingdom. The oral preparation (tablets) can be crushed, dissolved in water and given via orogastric or nasogastric intubation in patients that are unable to swallow; alternatively it can be administered per rectum using a feeding tube or Foley catheter for example. In the absence of methocarbamol, the management of patients with tremors is the same as for those with seizures.

The aim of treatment is to achieve adequate control of tremors; complete abolition of tremors is neither likely nor necessary and may require excessive drug administration.

Treatment often starts with the administration of **diazepam per rectum** at 1 mg/kg; this can facilitate intravenous catheter placement in seizuring/tremoring patients but may be omitted if a catheter can be rapidly placed without it.

- Proprietary rectal diazepam tubes may be used
- Injectable diazepam may be diluted with water or saline to increase the volume to be administered and then infused per rectum
    - Using injectable diazepam allows more accurate dosing but involves a greater time delay in preparation
    - Depending on the size of the animal, the use of a well-lubricated long intravenous catheter (with stylet removed), urinary catheter or nasooesophageal feeding tube will allow the diazepam to be administered more proximally in the rectum. This should minimise spillage from the anus and maximise drug absorption.
- The rectal mucosa has an extensive blood supply and drug absorption should occur readily so long as the solution is in contact with the mucosa and not mixed into faecal material.
- Intranasal diazepam administration has also been described although the author has no experience with this technique.
- Intramuscular midazolam has been used to treat children in status epilepticus and may have a role in the initial management of veterinary patients with seizures/severe tremors but this remains to be clarified.

Once an intravenous catheter is successfully placed, **additional diazepam can be administered intravenously** (0.5 mg/kg IV); in animals with severe poisoning it is common to see a marked but very transient positive effect. The diazepam bolus is typically repeated no more than twice more before additional treatment is instituted. In some cases it is sufficient to start the patient on a benzodiazepine infusion alone. In others patients, more intensive treatment is required although a benzodiazepine infusion may still be used to provide some skeletal muscle relaxation and reduce the required doses of other agents that may have more cardiorespiratory depressant effects:

- Midazolam is used most commonly: 0.1-0.5 mg/kg/hour (or 0.1-0.5 mg/kg IV as intermittent boluses)
- Diazepam: 0.1-1 mg/kg/hour

At the present time, **propofol** is usually the first agent of choice when management needs to be escalated. It is given as 2 mg/kg aliquots slowly intravenously until visible motor activity is alleviated. Propofol is then continued as a constant rate infusion initially at 3-6 mg/kg/hour but very much titrated to effect so that the patient is on the lowest rate necessary to prevent motor activity. Endotracheal intubation is performed and vital parameters monitored and recorded regularly.

Endotracheal intubation should be performed in all anaesthetised patients to protect the airway and prevent aspiration. Oxygen supplementation is not mandatory unless specific indications exist.

Propofol infusion:

The use of a syringe driver is preferred to allow accurate administration of a propofol infusion. However a solution of propofol in normal saline can be made and administered via a fluid administration set using an infusion pump. These patients are recumbent and immobile, and although not ideal, it may therefore be possible to manage them adequately without the use of a syringe driver or an infusion pump if one is not available.

There seems to be some debate about the use of **phenobarbital** in patients with suspected neuromuscular intoxication. If seizures are present, the seizure focus may persist for a short while but should resolve as the toxin is cleared from body so only short-term anticonvulsive therapy is needed.
On-going benzodiazepine therapy during propofol anaesthesia may suffice: anti-convulsive; cause better muscle relaxation and less respiratory depression than phenobarbital. Ultimately phenobarbital use may be matter of individual clinician preference and/or individual patient circumstances; perhaps especially indicated where propofol infusion cannot be administered.

Alternatives to propofol infusion:

If financial or practical constraints preclude the use of a propofol infusion, **pentobarbital** (short-acting barbiturate) boluses may be a viable alternative. However, to the author's knowledge, a sterile formulation of this agent for injectable use is no longer readily available (in the UK?) and the risks associated with using non-sterile preparations available for euthanasia must clearly be borne in mind and discussed with the owner.

- The recommended dose is 5-20 mg/kg slowly IV to effect (e.g. 3 mg/kg aliquots every 90 seconds)
- As barbiturates are cumulative, it is essential to monitor the patient closely for possible progressive and severe respiratory depression

Sterile pentobarbital preparations used to be used widely for the management of some neurological intoxication patients before propofol became available. Although the use of non-sterile formulations (used for euthanasia) is clearly not ideal, the risk-benefit assessment falls firmly on the side of benefit if euthanasia is the only other alternative due to financial constraints! Patients have been treated successfully using these non-sterile formulations with no apparent clinically significant complications related to lack of sterility.
Increasing anecdotal experience with the use of **medetomidine/dexmedetomidine** in this patient population but must be judicious (e.g. start with microdose medetomidine (e.g. 0.5-2 µg/kg IV as needed or 0.5-2 µg/kg/hour infusion)).

The use of **alfaxalone** may be considered but at least in the United Kingdom would be considerably more expensive than propofol. At this time there is much less experience with its use for neurotoxicity than for propofol but this may increase in time and it is certainly a viable alternative if, for example, propofol is in short supply. Dosing guidelines in dogs and cats are broadly similar and as follows:

- 2-3 mg/kg IV bolus, followed by
- 6 mg/kg/hour infusion titrated to effect

Thiopentone (barbiturate) and **inhalant anaesthetic agents** may also be considered.

As mentioned above, patients on a propofol infusion are usually also treated with on-going benzodiazepine (midazolam, diazepam) therapy. These agents cause muscle relaxation and act in a propofol-sparing capacity.

Discontinuing propofol infusion: there is no set-time frame as such for how long the patient needs to be kept on a propofol infusion; this is something that needs to be worked out on an individual patient basis. Generally an attempt is made to wean the patient off the propofol every 6-12 hours by reducing the infusion for example by 25% every 30 minutes (i.e. so weaning is done over 2 hours); if the patient is on a benzodiazepine infusion as well, this is typically continued unaltered until the patient is off propofol and then also weaned off gradually.

Intravenous fluid therapy may be required to correct hypovolaemia and/or dehydration. Fluid therapy is also indicated in the management of poisons that are nephrotoxic (e.g. non-steroidal anti-inflammatory agents) and those that are largely dependent on renal excretion. Oxygen supplementation is indicated in patients with respiratory compromise, for example from aspiration following vomiting, and in the contexts of certain poisons such as carbon monoxide.

Emergency database

An emergency database for the intoxicated patient may consist of one or more of the following if possible:

- Manual packed cell volume (PCV) and serum total solids (TS)
- Blood glucose, electrolyte, urea and creatinine concentrations
- Venous (or arterial) lactate
- Peripheral blood smear examination
- Electrocardiogram (ECG)
- Non-invasive blood pressure (NIBP)

It is recommended to perform an emergency database in all intoxicated patients although the timing of this should be governed by the facilities available and the emergency database must not be prioritised at the expense of emergency treatment. The exception to this is blood glucose concentration. Checking for hyper- or hyponatraemia and hypocalcaemia is also recommended if possible although these abnormalities are much less frequently implicated than hypoglycaemia as a cause of neurological signs in small animals.

Blood glucose concentration should be checked as soon as possible in all animals that present either seizuring or with marked neurological abnormalities. Clinical signs of hypoglycaemia usually relate to brain dysfunction due to neuroglycopaenia (i.e. reduced cerebral glucose availability) and to sympathetic nervous system stimulation. Depending on the severity of the hypoglycaemia, clinical signs range from mild (e.g. lethargy, weakness) to moderate (e.g. depression, ataxia, muscle tremors) to very severe (e.g. collapse, seizures, coma). Hypoglycaemia (probably only moderate-to-severe) can also cause sinus bradycardia/bradydysrhythmia.

The blood glucose levels at which signs develop can vary between individuals, but in general:

- Clinical signs usually do not occur until blood glucose is < 3 mmol/l
- Secondary neurological signs are unusual while blood glucose > 1.5-2 mmol/l

The appropriate treatment for hypoglycaemia depends on the blood glucose concentration, the clinical signs, and in some cases the cause and suspected chronicity.

Topical mucosal therapy:

- Either a proprietary topical 'fast acting' glucose solution (e.g. Glucogel®, BBI Healthcare) or sugary water or honey for example can be applied to the gums or other mucosal surfaces.
- This route of treatment is unlikely to resolve the hypoglycaemia but may alleviate clinical signs sufficiently while other routes of intervention are instigated.
- Dosing is usually empirical.

Enteral therapy:

- Enteral therapy may be adequate in less severe cases and is the most physiological route of supplementation
- Patients are fed small amounts of palatable food regularly (e.g. every 1-2 hours) and in some cases sugar solutions, honey or similar are included.
- Contraindications for enteral therapy include inability or refusal of the patient to eat voluntarily, absent gag reflex, obtundation or vomiting.

Parenteral therapy:

- More severe cases of hypoglycaemia require more aggressive intervention in the form of parenteral therapy; this is usually intravenous but intraosseous administration may be required in some cases.
- Glucose is administered until clinical signs are controlled but a starting dose of 0.25-0.5 g/kg is usually recommended – this is equivalent to 0.5-1.0 ml/kg of a 50% glucose (dextrose) solution.

- 50% glucose solution should be diluted (e.g. with an equal volume of crystalloid solution) prior to administration as it can cause venous irritation and inflammation (phlebitis).
- Clinical signs usually resolve quickly with treatment
    - Occasionally animals that are showing signs of brain dysfunction, including seizures, continue to do so despite establishing normoglycaemia – signs may or may not eventually abate. This phenomenon may be due to continued neuroglycopaenia despite normoglycaemia or due to residual injury suffered during the hypoglycaemic period.

Following bolus administration of glucose (which can be repeated), a glucose infusion is usually required to prevent recurrence of clinical signs. Some glucose solutions for infusion are available commercially (e.g. 0.9% sodium chloride + 5% glucose) but they can also be readily constituted.

Glucose solutions for long-term infusion are usually of 2.5% or 5% concentration. Occasionally it is necessary to administer a 10% glucose solution. The tonicity/osmolarity of this solution may pose a risk of phlebitis when administered via a peripheral vein and if possible it is recommended to infuse through a central vein (larger blood flow and more rapid dilution reduce the risk of localised adverse effects on the vessel).

Treatment of hypoglycaemia should be guided by clinical signs and if available, regular monitoring of blood glucose concentration.

Additional tests that may be indicated at the appropriate time in certain poisoned patients include acid-base analysis, urinalysis (e.g. oxalate crystals in ethylene glycol poisoning) and calcium measurement (e.g. hypocalcaemia may occur in ethylene glycol poisoning). Abdominal radiographs taken at the appropriate time may reveal ingestion of items containing heavy metals or certain enteric-coated or sustained-release drug formulations. Routine haematology and biochemistry profiles may become indicated as case management progresses and may also identify pre-existing conditions that may have implications with respect to management of individual patients.

Coagulation testing may also be indicated in some cases. It should always be performed in coagulopathic animals with suspected anticoagulant rodenticide or xylitol poisoning. Since factor VII has the shortest half-life, the extrinsic coagulation pathway is affected first, so prothrombin time (PT) is prolonged before and more severely than activated partial thromboplastin time (aPTT)in rodenticide poisoning. If the animal is experiencing haemorrhagic diathesis both PT and aPTT will be prolonged. If facilities to perform PT/aPTT are not available in-house, and a significant delay is anticipated in obtaining the results, activated clotting time (ACT) can serve as a useful screening test in animals with clinical evidence of haemorrhage. A tube containing dichotomous earth (e.g. Fuller's earth) and facilities to warm the tube (to 37^0C) is all that is required for this test.

Lactate:

Extreme muscle activity (e.g. seizures, trembling/tremors) may cause hyperlactataemia due to relative oxygen deficiency (energy requirements greater than aerobic metabolism can provide) and increased glycolysis. This abnormality usually resolves quickly once stabilisation has been achieved. Unless physical perfusion parameters are also suggestive of hypoperfusion, this raised lactate should not prompt aggressive fluid therapy for presumed hypovolaemia.

Gastrointestinal decontamination (GID)

Toxin exposure is usually via ingestion and gastrointestinal decontamination (GID) is frequently indicated. This consists of emptying of the stomach followed by administration of an adsorbent to minimise absorption of any poison remaining in the gastrointestinal tract. Cathartics used to be used in the past but seem to have fallen out of favour to some extent more recently.

It should be noted that as is often the case with veterinary, and sometimes, human medicine there is little in the way of evidence base for many of the decisions made in the treatment of some poisonings and opinions vary between the relative merits of one approach versus another, whether gastric emptying or just activated charcoal should be used, for which poisons activated charcoal should be used and so on.

Gastric emptying:

In the absence of contraindications, induction of emesis is the most expeditious means to empty the stomach; feeding a small meal first may increase the effectiveness of this approach. Older resources used to say that gastric emptying should only be performed if the patient presents within 2 hours of poison ingestion. However clinical experience suggests that sometimes significant decontamination can be achieved even up to 6 hours post-ingestion so a less limited approach is recommended nowadays. Drugs used to induce emesis are summarised below.

Drugs used to induce emesis [C – cats, CNS – central nervous system, D – dogs]

Drug	Dose	Comments
Apomorphine	D: 0.02-0.1 mg/kg SC, IM, ocular (IV)	Drug of choice, emesis usually in 5-15 minutes Centrally-acting Protracted vomited occurs sometimes Sedation, respiratory depression, ataxia possible but relatively rare Naloxone reverses CNS and respiratory-depressive effects but not dopaminergic emetic effects Experimental pharmacokinetic study suggests 'topping up' initial dose may not induce emesis but could exacerbate sedation; however clinical experience suggests it does induce emesis Ocular route: apply to conjunctival sac; lavage thoroughly with saline following emesis to minimise drug absorption; highly dependent on compliance but can be quite successful; both tablets dissolved in water and injectable preparations have been used by this route
Apomorphine	C: 0.01-0.02 mg/kg SC, IM (IV)	Use lowest possible dose Not recommended by some due to possible significant sedation Naloxone reverses CNS and respiratory-depressive effects but not dopaminergic emetic effects
Medetomidine	C: 20 µg/kg IM, IV	Alpha$_2$-adrenergic agonist Use atipamezole to reverse effects once emesis has occurred Use very cautiously due to potential cardiorespiratory depression; sedated cats that have not vomited are often reported!
Xylazine	C: 0.4-0.5 mg/kg IM, SC	Alpha$_2$-adrenergic agonist Effects reversed by yohimbine – availability? Atipamezole may also reverse effects Use very cautiously due to potential cardiorespiratory depression Clinical use may be limited by restricted availability in small animal-only practices

See Appendix 1 for a blog post on inducing emesis in cats from July 2014.

As mentioned previously, **contraindications to inducing emesis** include:

- Significantly altered mentation due to increased risk of aspiration of vomitus; in particular in depressed animals in whom there may be dysfunction of the gag reflex
- Respiratory distress and pre-existing conditions (e.g. laryngeal paralysis) that may predispose the animal to aspiration
- Animals that are already vomiting
- Ingestion of a caustic or corrosive agent (e.g. acids or alkalis) – emesis will potentially expose the oropharyngeal and oesophageal mucosa to further injury. Consumption of milk or water should be encouraged if not contraindicated to dilute the poison.

Administering anti-nausea/anti-emetic medication following successful gastric emptying:

Although inducing emesis is a quick and effective means of gastric emptying, vomiting is clearly an unpleasant experience and some patients may vomit for a protracted period; this can be witnessed by repeated episodes of vomiting with only small amounts of frothy/bilious material produced and a nauseous sorry-looking patient! As such, once the patient has vomited sufficiently that gastric decontamination has occurred, anti-nausea/anti-emetic medication may be administered. Furthermore this may allow activated charcoal administration to commence sooner as well. Apomorphine acts as a dopamine agonist stimulating the chemoreceptor trigger zone to cause vomiting; metoclopramide is a dopamine antagonist and may therefore be the most sensible anti-emetic drug after apomorphine use and is now licensed in dogs and cats (Vomend®, Eurovet). Maropitant (Cerenia™, Pfizer Animal Health) is a neurokinin-1 receptor antagonist that is also licensed in dogs and cats and is an alternative option here; however it is typically more expensive than metoclopramide and a single dose lasts for 24 hours which is unnecessary in these patients.

Gastric and colorectal lavage:

In patients in which induction of emesis is contraindicated or unsuccessful, gastric lavage may be appropriate for gastric emptying. However it is contraindicated following ingestion of caustic or corrosive substances and where the risks of general anaesthesia are considered unacceptable. In some cases (e.g. metaldehyde poisoning), following gastric lavage, the author will perform additional lavage via a stomach tube inserted as proximally as possible per rectum. Colorectal lavage is continued until clear fluid is returned and activated charcoal suspension is then instilled. The anus may be plugged with a swab for example for a short period of time to minimise leakage of the activated charcoal.

Activated charcoal:

Activated charcoal acts as an adsorbent binding to toxins and allowing their passage through the gastrointestinal tract while preventing or minimising further systemic absorption. It is typically administered once gastric emptying has been performed and should be given as soon as possible. If an emetic has been employed for gastric emptying enough time must be allowed for the emetic effects to subside before activated charcoal is administered; administering an anti-emetic to facilitate this is an option. In some cases activated charcoal is administered initially via stomach tube at the end of gastric lavage.

Different substances are bound to different degrees by activated charcoal, and potentially not at all in some cases. However, detailed information on this is relatively limited. Unless contraindicated, the use of activated charcoal in almost all cases of oral poisoning is probably reasonable and may also help following topical poisoning (see below). Activated charcoal should not be used following ingestion of caustic or corrosive substances, in patients that are vomiting or seizuring, or where there is any possibility of gastrointestinal perforation/obstruction/ileus. It should also potentially be avoided if oral medications or antidotes are needed and if gastrointestinal endoscopy or surgery is likely in the near future. Vomiting and constipation following administration of multiple doses are the main complications reported.

Hypernatraemia due to osmotic effects with movement of water from the circulation into the gastrointestinal tract is a potential adverse effect that is suspected to be rarely clinically significant but more information is needed and it is more likely when using products that also contain sorbitol. It can be avoided by close attention to fluid balance as indicated.

The recommended dose in dogs and cats is 1-5 g/kg to be repeated as necessary (typically every 4 to 6 hours) until black faeces are detected; in theory the ratio of activated charcoal to toxin should be 10:1, but in reality the amount of toxin in the gastrointestinal tract is rarely/never known. Doses up to 8 g/kg have been used. However given the concern mentioned above regarding possible hypernatraemia, a rational approach is probably to use low doses accurately measured and at well-spaced out intervals, and to not administer this product to patients that are either already dehydrated or have been exposed to a poison that may itself induce hypernatraemia. Activated charcoal is often successfully administered in food to dogs. However compliance is likely to be much poorer in cats and a risk/stress-benefit assessment should be made on an individual case basis. Various proprietary preparations are available with accompanying dosing guidelines, including powdered formulations (e.g. BCK Granules®, Fort Dodge) that can be added to food or made into a slurry and administered by mouth, and suspensions (e.g. Charcodote®, Pliva Pharma Ltd).

Topical poisoning

Washing the patient is recommended to minimise irritation of and absorption via the skin; this should also minimise absorption through ingestion following grooming. Washing is usually done using mild soap or detergent followed by copious rinsing with water and then drying the animal as thoroughly as possible. Powdered toxins may be vacuumed off before washing. All individuals involved in handling the animal should take care to wear gloves and preferably an apron so as to avoid self-contamination. In some cases it may be appropriate for the owner to wash the animal at home. However in compromised or non-compliant animals, veterinary care is recommended.

Clipping the coat of long-haired patients may help to maximise decontamination. Chemical restraint may be preferable during washing to allow protection of the eyes and in some cases general anaesthesia with endotracheal intubation is safest to minimise the risk of aspiration. Vital parameters including rectal temperature should be monitored closely throughout.

Oily substances may be more successfully removed using commercial hand-cleaning degreaser formulations (e.g. Swarfega Hand Cleaner® products) but it is important to ensure that such preparations are thoroughly washed off the animal subsequently.

Sticky substances (e.g. glues, paints) can be removed from the coat by applying butter or margarine (the contaminant dissolves in the high fat medium) and then washing off with soapy water. Otherwise allow the contaminant to dry in situ and then clip the fur off.

The use of activated charcoal is generally recommended following topical poisoning. This is to minimise gastrointestinal absorption that may occur following ingestion from grooming. In addition, some poisons undergo enterohepatic circulation following absorption from the skin and thereby become available in the gastrointestinal tract.

In cases in which the skin has come into contact with an acidic or caustic substance, the affected area should be very thoroughly lavaged (‘the solution to pollution is dilution’) using normal saline or indeed warm water; use of other agents may result in neutralisation with the associated chemical reaction causing skin burns. The same is true in cases of ocular contamination and in both cases the animal should be appropriately analgised and chemically restrained to allow comprehensive lavage to be performed. Damaged skin is highly susceptible to mechanical injury and gentle lavage is therefore mandatory.

Diuresis

Diuresis is most indicated in the treatment of poisoning by agents for which renal excretion of either the primary intoxicant or its metabolites is a significant feature (e.g. NSAIDs, salicylates, phenobarbital). Standard intravenous isotonic crystalloid therapy is employed to promote renal excretion with or without additional diuretic administration. Isotonic crystalloid therapy is administered at a rate of 1-4 mL/kg/hour above calculated fluid requirements and the patient must be monitored closely to ensure that adequate urine production occurs. In cases of aggressive diuresis, close monitoring of hydration status and electrolyte concentrations is indicated.

Antidotes

In a significant proportion of canine and feline patients a diagnosis of poisoning is made presumptively with the poison in question remaining unknown. Furthermore, specific antidotes or antagonists do not exist for the majority of potentially poisonous substances to which dogs and cats may be exposed. That said, the majority of clinical cases reported are due to a relatively small number of poisons for which in some cases specific treatments are available. Intravenous lipid emulsion is an antidotal therapy that is gaining increasing impetus (see below).

Examples of poisons and their antidotes include:

Poison	**Antidote**
Benzodiazepines	Flumazenil
Cardiac glycosides (including *Bufo* toad toxicosis)	Digoxin immune Fab (Digibind)
Cyanide	Hydroxycobalamin (Cyanokit) – vitamin B12 precursor
Ethylene glycol (antifreeze)	Fomepizole (4-MP) or ethanol
Iron	Deferoxamine – iron chelator
Lead	Succimer (2-3-dimercaptosuccinic acid)
Muscarinic mushrooms	Atropine
Opioids/opiates	Naloxone (Narcan)
Organophosphates	Atropine for muscarinic signs; 2-PAM (Paralidoxime) for nicotinic signs
Paracetamol (acetaminophen)	N-acetylcysteine
Serotonin syndrome caused by serotonergic substances	Cyproheptadine may help
Vitamin K antagonist anticoagulant rodenticides	Vitamin K_1
Zinc (and other heavy metals, e.g. copper, mercury, lead)	D-penicillamine

Toxicological testing?

In a significant number of dogs but also cats poisoning is unwitnessed and patients are treated based on suspicion or presumption. As such being able to perform toxicology and poison testing on some form of body fluid/tissue to confirm the diagnosis on the face of it seems very attractive. However there are some considerations to bear in mind:

1. Availability of testing: this has traditionally been very limited; in some cases it has been possible to make use of human diagnostic laboratories but infrequently. In the United Kingdom for example a new service is available (Carmichael Torrance Veterinary Diagnostic Laboratory, http://ctdslab.co.uk/toxicology-and-poison-testing/) which employs gas chromatography mass spectrometry and offers a variety of options e.g. wide-ranging small animal toxicology panel; screening for groups of agents (e.g. vitamin K antagonist rodenticides, drugs of abuse); single agent screening.

This laboratory also offers 'sudden death investigation' in the form of post-mortem +/- toxicology screening. Clearly it may be that whatever poison is involved in a particular case, ante- or post-morten, is not one the laboratory can test for.

2. Practicalities of testing: are the samples that are required ones that can be realistically/safely obtained and can they be reasonably transported to the laboratory, e.g. is freezing required, is immediate transportation required, etc.?
3. Time delay in obtaining results: this is a major drawback in the context of managing actual on-going clinical patients as by the time results are obtained most poisoned patients will either be improved/normal or potentially will have been euthanised/died. For example results from the laboratory mentioned above can be expected 'within five days'.
4. Will the results actually matter? Confirming poisoning may clearly be considered important for a variety of reasons e.g. to confirm a clinical suspicion, to afford pet owners additional information, to prevent repeat exposures, to facilitate investigations etc. However it is important to bear in mind that in many cases poisoned patients are managed symptomatically according to their clinical syndromes and progression and antidotes are not available for a significant number of potential poisons. As such even if results could be obtained within a clinically helpful timeframe they may not in fact alter clinical management – but they of course might and would at least help confirm the suspicion!

Intravenous Lipid Emulsion (ILE)

The use of intravenous lipid emulsion (ILE) for intoxication was originally investigated experimentally in the 1970s and 1980s. Subsequently there have been a growing number of case reports of its use in clinical patients first in human medicine and more recently in veterinary medicine, mostly relating to the treatment of haemodynamically or neurologically-significant poisonings. Early reports in humans focused on treatment of local anaesthetic systemic toxicity (LAST) – for which it has now become a fixed part of the treatment approach – but the use of ILE in people has now been reported for a wide variety of drugs and other toxic substances. Further clinical studies are needed to determine the safety, effectiveness and risk:benefit ratio of this therapy but a growing number of experimental studies and case reports suggest that ILE may become a valuable addition to the veterinary clinician's emergency drug arsenal.

Intravenous lipid emulsion

A variety of lipid emulsion preparations have been used clinically for several decades for example in parenteral nutrition or as a vehicle for delivery of lipid-soluble drugs (e.g. propofol). ILEs are oil-in-water emulsions consisting of triglyceride-containing oils, a phospholipid emulsifier (10% or 20%), and glycerin. Although others are available, the most commonly used preparation for treating toxicosis at the moment is Intralipid 20% which is a soybean-oil-based emulsion of long-chain triglycerides.

The fat droplets in ILEs are similar to endogenous chylomicrons and are cleared by skeletal muscle, splanchnic viscera, myocardium, and subcutaneous tissues. Glycerol and free fatty acids are the breakdown products of the triglyceride, phospholipid, and choline components of ILE and are used by body tissues as energy sources.

Mechanisms of action

The precise mechanism of action through which ILE increases the rate of recovery and augments conventional resuscitation efforts in various cases of lipophilic drug toxicosis is currently unknown. It may be that this treatment has several potential mechanisms of action and one or more may be involved to a greater or lesser degree depending on the specific toxin in question. Current theories regarding ILE's main mechanisms of action are thought to relate to a 'lipid sink' sequestration effect and/or a metabolic effect that improves cardiac performance; however other mechanisms of action are also likely.

***'Lipid sink'* effect:**

At this time it is thought that the 'lipid sink' effect is likely to be the predominant mechanism. This theory suggests that administered lipid remains in the circulation where it physically binds to circulating toxin thereby trapping it in the plasma and reducing the free concentration of the toxin, i.e. the toxic compound is sequestered into a lipid compartment within the bloodstream. As the ILE circulates throughout the body, fat droplets containing the toxin are cleared by skeletal muscle, splanchnic viscera, myocardium, and subcutaneous tissues, which help dilute and clear the offending toxin from the body. Trapping the toxin in the circulation means that there is less available for binding to tissue and organ receptors with subsequent toxic effects. Moreover in some cases it may be that the 'lipid sink' effect is strong enough to actually pull lipophilic toxins away from their sites of action into the circulation, especially from the heart and brain. In other words the lipophilic toxins move down their concentration gradient away from the tissues and into the circulation where they are then trapped in the lipid sink.

The degree of lipid solubility of a substance, referred to as its lipid partition coefficient, may affect the clearance rate of the offending toxin following ILE administration. Given the 'lipid sink' mechanism of action, it makes sense that lipid emulsions may be most effective in the treatment of intoxication with substances that have high lipid solubility.

The time frame (acute versus chronic) that ILE may prove beneficial in treatment may depend on the individual toxin's half-life. If the toxin's detrimental side effects are the result of a metabolite formed from the toxin, then ILE therapy may or may not be beneficial unless it is given in the acute setting to decrease metabolite formation.

'Redistribution':

Another suggested mechanism of ILE as an antidote, instead of or in addition to sequestering toxin in the bloodstream, is that it may augment distribution of the toxin to fat soluble tissues rather than biologically active sites, i.e. so the toxin is not trapped in the circulation but it is instead taken up by tissues in which it is not biologically active.

Improved cardiac performance:

The beneficial effects of ILE therapy may be linked to improvements in cardiac function through either the direct benefit (e.g. utilisation of free fatty acids as an energy source by the myocardium, an increase in intracellular calcium) of lipids on the myocardium or the reversal of cardiovascular dysfunction caused by the specific toxicant.

Veterinary indications

ILE has been used as an antidote in human medicine for actually quite some time – maybe 15 years or so – but it is definitely true to say that it took some time to gain wider recognition. One of the issues that is often discussed when it comes to medical practice is the so-called 'knowledge translation gap'. What this means is that people start reporting a potentially new and even game-changing therapy but it can take quite some time, often years, before this therapy becomes part of the practice of clinicians on a widespread basis. And this relates to issues of delays in publication, access to publications and so on; on the plus side with the increasing use of social media and free open access education there are definitely moves towards cutting the delay in knowledge translation.

In humans ILE was first used for treating local anaesthetic systemic toxicity and that is the most established of its uses. And in fact there are societies and bodies such as the American Society of Regional Anaesthesia that have produced guidelines for the use of ILE in LAST. And then ILE started to be used for other intoxications – mostly drug-related but not exclusively. What is interesting is that somewhat unusually nowadays intravenous lipid emulsion as an antidote has not undergone the sorts of phased clinical trials that maybe we would have expected it to. If we look at the published literature in human medicine it is surprising to see how little there is relatively speaking. Although this is speeding up a little at the moment in 2014 there are no prospective randomised controlled trials looking at the use of ILE as an antidote and there certainly aren't any metanalyses or systematic reviews. We are basically talking about a number of case reports and last year (2014) a case series of 48 cases from the Lipid Registry was reported.

So what about the veterinary literature? If you research the veterinary literature you will find around 14 case reports or series with the first published in 2009; there is also a large retrospective case series of baclofen poisoning in dogs and cats in which the use of ILE is mentioned for some of the cases. And then there are three clinical practice review-type articles.

Now again as with the human literature all of the veterinary studies are single case reports or very small series and the vast majority are retrospective in nature. There are no powered prospective randomised controlled trials. There are certainly issues that we have to be aware of in terms of generalising case report data to all our patients. Also there is this concept of publication bias where people are less inclined to report, and especially journals are less inclined to publish, cases in which a positive effect is not seen, i.e. negative cases. In the human literature on ILE, reports of successful outcome significantly outweigh those of treatment failure. And perhaps all one can really say is that there is a view that ILE is associated with improvement in some cases without establishing this as a causal relationship.

Many reports discussing the use of ILE as an antidote still refer to it as an 'experimental' therapy. And the reason for this is that there has been no "proper" phased clinical introduction and evaluation. Having said that in veterinary medicine ILE is so not alone in that regard and we don't persist in referring to the myriad other drugs that we use without a proper clinical basis as experimental!

LAST is relatively rare in veterinary patients but ILE should be used in the treatment of cases in which it occurs. In veterinary medicine, ILE is generally considered in the treatment of toxins with a high morbidity or known potential for mortality, especially if traditional therapies are proving to have limited efficacy or are cost prohibitive – the latter can often prompt requests for euthanasia. ILE can have adverse effects (see below); however it is relatively safe and it is typically used when the risk-benefit assessment falls on the side of potential benefit being greater than potential risk. Response to treatment can vary from no apparent efficacy through to complete resolution of clinical signs and the lipid solubility of the toxin in question is thought to be a major factor in determining efficacy. Anecdotal reports of successful use of ILE in the management of veterinary patients are becoming more commonplace, but until controlled clinical studies are published caution should be taken to avoid viewing ILE as a "silver bullet" with guaranteed results and to remember that essentially it is still an experimental therapy.

Toxins for which ILE is currently recommended to be considered include:

- Baclofen
- Macrocyclic lactones (e.g. ivermectin, moxidectin, milbemycin; out of interest, moxidectin is reported to be 100 times more lipophilic than ivermectin)
- Metaldehyde
- Pyrethrins
- Beta-blockers (especially the more lipophilic ones such as propanolol)Calcium channel blockers
- Cyclobenzaprine (a human muscle relaxant)
- Local anaesthetics
- Psychotropics (selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), cyclic antidepressants)
- Ibuprofen? (single case report in 2014)*
- Tramadol?

There are also anecdotal reports of its use for e.g. tremorgenic mycotoxins, strychnine. It is notable that a lot of the drugs/toxins for which ILE has been used are ones that cause neuromuscular signs or haemodynamic compromise as part of their toxidrome. It is likely that in time this list will grow as more evidence is acquired. As always, prior initial stabilisation of the patient if possible is essential, especially with respect to cardiovascular status, and ILE should be considered supplementary to, rather than a substitute for, traditional therapies.

(* There is thus far a single case report published of a dog that had ingested a very large amount of ibuprofen that had resulted in severe neurological and some haemodynamic compromise as can occur with NSAIDs in very high overdoses. The dog reportedly started to improve three hours after ILE administration and went on to make a full recovery. Furthermore plasma ibuprofen levels were measured before and after ILE administration; a high toxic level was detected prior to ILE that had reduced to zero after ILE administration; there is no mention in the paper about any interference ILE-induced lipaemia could have on this analysis. Potentially at this time it may not be a case of using ILE in every case of NSAID intoxication as standard therapies usually result in a successful outcome, but reserving ILE for the more extreme cases?)

Dosing guidelines

At this time ILE is used off-label in veterinary patients and much information has been extrapolated from use in human medicine. Optimal treatment protocols will likely vary between toxins and possibly species; however, currently this information is not available. Several different ILE infusion protocols have been published all using 20% lipid solutions; there have been no safety studies evaluating the use of ILE in the clinically poisoned veterinary patient, and careful monitoring and risk assessment is important.

Protocol using Intralipid 20%:

- Administer 1.5 ml/kg as a slow IV bolus over 2-3 minutes; follow with CRI 0.25 ml/kg/min for 30-60 minutes
- Monitor serum every 2 hours
- If patient remains symptomatic:
    - Can repeat bolus and infusion dose as above when serum becomes clear (non-lipaemic)
        - If no improvement after 3 doses (bolus + infusion), discontinue ILE treatment
    - Do not repeat ILE if serum is very orange or yellow
- Monitor patient until clinical signs resolved and serum no longer lipaemic in case signs return once the lipid has been metabolised

As commercially available ILE preparations are isotonic, they can be safely administered through a peripheral intravenous catheter.

Although relatively large volumes of ILE are given in a short space of time, it is worth noting that the total amount of lipid infused per 24 hours in toxicological applications is still lower than the maximal amount recommended for parenteral nutrition administration.

Usage guidelines

Unopened ILE is generally stored at room temperature and an unopened container will have a shelf life of up to 2 years. Specific indications for storage vary depending on the manufacturer, type of emulsion, and packaging. When using these products, strict aseptic techniques are imperative to prevent risk of bacterial contamination of the ILE, resulting in potential bacteraemia, but also destabilisation of the emulsion. Preparations should not be used after their shelf-life has expired.

Once opened and/or mixed with other fluids, ILE should be refrigerated between uses and used within 24 hours. If prolonged therapy (> 24 hours) is required, a new bag or vial must be used.

There is also some evidence – experimental at the time of writing (Nov 2014) – that ILE can be administered intraosseously to good clinical effect.

Adverse effects

Hypertriglyceridaemia and lipaemia are unavoidable, but typically transient and inconsequential, developments with the use of ILE. ILE has a high safety margin; adverse effects are uncommon but may be caused by contamination of the lipid product or direct reaction to the emulsion. There are very few reports thus far in clinical patients. The choice between potential or theoretical adverse side effects of ILE versus consequences of an unsuccessful resuscitation is clear. Obviously, ILE should be considered on a case-by-case basis including a careful assessment of risk versus benefit. Nevertheless caution should be exercised in estimates of safety based on low overall numbers. Serious adverse events with any drug therapy may be rare and require many thousands of administrations to identify an effect which holds clinical significance.

Contamination:

As ILE preparations are rich in nutrients contamination is a concern although this is less when they are used in isolation as opposed to in total parental nutrition formulations. Contamination may occur due to poor handling and aseptic technique and may result in local or systemic infection.

Direct reaction:

Direct reactions to ILE are reportedly rare but may be acute (anaphylactoid hypersensitivity reaction) or delayed/sub-acute (‘fat overload syndrome’); the latter is usually the result of the administration of excessive volumes or high administration rates overwhelming the endogenous lipid clearance mechanisms. In people, FOS can result in fat embolism, hyperlipidaemia, hepatomegaly, icterus, splenomegaly, thrombocytopenia, increased clotting times and haemolysis; no information is currently available from veterinary patients apart from one report of presumed ILE-induced haemolysis in a dog that recovered fully with appropriate management.

Other potential adverse effects:

Other potential adverse effects, including pancreatitis, are possible but it should be stressed that in general adverse effects to ILE therapy are considered rare; with respect to pancreatitis a possible increase in serum amylase may occur following ILE administration but this finding should not be equated with pancreatitis and the diagnosis should be made by other better means. Currently there are no published reports of this but the potential for ILE to 'trap' drugs (e.g. anticonvulsants) being used therapeutically must be borne in mind and may be suspected if clinical deterioration is associated with ILE administration. ILE-induced lipaemia may interfere with laboratory tests and ILE causes false elevations in blood glucose concentrations with certain glucose analysers. Although the impact of ILE use on laboratory analysis is often listed as a 'complication' the author would not necessarily label it in this way; it is an undesirable consequence of the use of ILE that can potentially have clinically significant consequences in the management of some patients, but perhaps not a 'complication' per se. There is some discrepant evidence but ultracentrifugation of blood samples may allow laboratory tests to be performed after ILE use. In human medicine there are a very small number of case reports in which the use of ILE and the development of acute respiratory distress syndrome (ARDS) has been temporarily associated but of course this does not mean that ILE use caused the ARDS, i.e. association is not the same as causation. Concern has recently been raised that increasing blood carriage capacity for toxin in the absorptive phase of intoxication with early administration of ILE might increase absorption from the gastrointestinal tract paradoxically increasing intoxication; again this remains speculative at this time. In 2014 two cases of asystole that developed very soon after ILE administration were reported but again it was impossible to attribute causation rather than temporal association to these scenarios, i.e. did ILE administration cause the asystole or was it coincidence in patients that were clearly very sick. In both cases spontaneous circulation returned within a few minutes of asystole with CPR (although both patients died subsequently in hospital).

A 20% lipid emulsion is preferred over the 10% lipid emulsion due to the higher proportion of free phospholipid available in the 10% formulation. Free phospholipids are thought to increase the potential for adverse effects due to their interference with lipoprotein lipase activity, which decreases ILE clearance. Large volumes of lipid emulsion are required for effective treatment. Propofol is therefore not recommended for use as an ILE formulation due to the high amounts of anesthetic that would be delivered with its lipid emulsion vehicle

Interested individuals can explore the use of lipid emulsion therapy further here: http://www.lipidrescue.org/

Neuromuscular toxins

Metaldehyde (Slug bait)

Metaldehyde is a cyclic tetramer of acetaldehyde that is commonly used as a pesticide against slugs and snails (molluscicide). Commercial pellet preparations usually contain 1.5-8% metaldehyde w/w in a cereal base. The pellets are often blue or green in colour and the cereals and other additives make slug/snail baits palatable to dogs. Cats as usual are more discerning and metaldehyde poisoning has only been reported in a few cases; the information provided in these notes is essentially applicable to both species. Liquid preparations containing higher concentrations of metaldehyde are also available as are granular and powdered preparations. Metaldehyde baits sometimes contain additional herbicides and pesticides, most commonly carbamate insecticides. Metaldehyde may also be found in fuel packs for camping stoves.

Toxic dose

A fatal oral dosage of metaldehyde in dogs of 60 mg/kg body weight has been reported although some authors quote much higher values. Clinical signs may be expected to occur at a range of typically much lower dosages. A lethal dose of 207 mg/kg has been reported in cats. As always, check with poisons information resources for the most recent information.

Toxicokinetics

Metaldehyde may be absorbed intact from the gastrointestinal tract but its subsequent distribution, metabolism and excretion remain to be fully clarified. Acid hydrolysis occurs in the stomach producing acetaldehyde which is then absorbed rapidly and converted to carbon dioxide (probably eliminated via the lungs) or excreted in urine. The half-life of metaldehyde in people is estimated at approximately 27 hours but is unknown in dogs.

Mechanism of toxicity

The precise mechanism of toxicity of metaldehyde remains to be elucidated but it is known to readily cross the blood-brain barrier and impairment of GABA activity is currently thought to be most implicated. As GABA is an inhibitory neurotransmitter a decrease in its activity may be responsible for the increased neurological activity seen in metaldehyde poisoning. A decrease in the concentration of other neurotransmitters in the central nervous system, such as serotonin (5-HT) and noradrenaline, may also be involved.

Clinical signs

Clinical signs due to metaldehyde poisoning often occur quickly (e.g. within 30-60 minutes of ingestion) but may take up to several hours to appear. The typical presentation involves central nervous system and muscular signs including twitching, tremors, muscle spasms and hyperaesthesia, with opisthotonos and seizures (including status epilepticus) being seen in severe cases. Hyperthermia is frequently identified in metaldehyde poisoning and presumed to occur due to the marked neuromuscular activity (hence it is sometimes referred to as the 'shake and bake syndrome'). Hyperthermia may contribute significantly to the pathophysiology and clinical presentation.

Case management

As above under 'Initial stabilisation – treatment of seizures and muscle tremors'.

It is important to check blood glucose concentration in any animal presenting with central neurological signs. In metaldehyde poisoning, normo-, hyper- or hypoglycaemia (typically only mild) may be seen.
Likewise excluding sodium and calcium abnormalities in particular may be appropriate according to the patient's history.
Hyperlactataemia may be present and is most likely to be due to extreme muscle activity (relative oxygen deficiency) rather than hypoperfusion (absolute oxygen deficiency).
A minimum emergency database should be performed at the appropriate time.

Treatment of metaldehyde poisoning should always be instituted as early as possible and should be aggressive. A conservative approach in a dog with severe neurological signs may result in preventable irreversible brain injury and potentially respiratory failure. **Induction of emesis is only appropriate in asymptomatic animals and *dogs showing neuromuscular signs should be fully anaesthetised and subjected to thorough gastric and colorectal lavage* including activated charcoal deposition**.

External stimulation should be kept to a minimum (e.g. cotton wool balls/swabs in the ears, dim lighting, minimise noise and passage of personnel). Fluid therapy and appropriate nursing measures should be instituted throughout.

Metaldehyde is lipid soluble and it is probable that intravenous lipid emulsion (e.g. Intralipid®) therapy has a role to play in treating these patients. Limited anecdotal experience support this suggestion although at the time of writing, to the author's knowledge, there is no published information in either experimental or clinical settings in human or veterinary medicine. The prognosis for metaldehyde poisoning with standard treatment is good and survival rates are high. As there is currently no published evidence that ILE therapy is effective in metaldehyde poisoning, it can be argued that its use at this time is probably best reserved for cases where either euthanasia on financial grounds seems increasingly likely, i.e. due to on-going costs associated with standard treatment, or where clinical signs are really very severe. ILE therapy is generally considered to be safe with little risk but there are potential adverse effects and as such a risk-benefit assessment is always indicated for what is still considered an 'experimental' treatment. The author has a special interest in ILE therapy and takes a more liberal view to its use in metaldehyde poisoning.

Clinical signs may persist for 24 hours or more; usually less than 48 hours. The prognosis for full recovery is good and survival rates are very high for animals that receive prompt and aggressive management and survive the initial 24-hour period following intoxication. Dogs recovering from severe metaldehyde intoxication may very occasionally have temporary blindness and liver failure is a serious but very infrequently reported delayed (2-3 days) development.

Pyrethrins/Pyrethroids

Sources

Pyrethrins are naturally occurring insecticidal esters of chrysanthemic acid and pyrethric acid extracted from the *Chrysanthemum cinerariaefolium* plant; pyrethroids (e.g. permethrin) are synthetic pyrethrins. Many topical and household insecticidal preparations containing these compounds are marketed for the control of flea and lice infestations amongst others in dogs and cats. These preparations are widely available from a variety of outlets.

Synthetic pyrethroid insecticides are now most commonly used in small animal patients as topical spot-on formulations and the accidental or misguided inappropriate use of canine products on cats is the most commonly encountered cause of poisoning. In addition cats may directly contact or lick the product once applied to a dog in the household including from the dog's bedding.

Toxic dose

The toxic dose for permethrin in cats is unknown. Dermal application of 100 mg/kg permethrin may prove life-threatening if untreated. As always, check with poisons information resources for the most recent information.

Mechanism of toxicity

Pyrethrins and pyrethroids alter the kinetics of neuronal sodium channels causing repeated nerve firing. In addition some of these compounds may also inhibit gamma aminobutyric acid (GABA) receptors resulting in hyperexcitability of nervous tissue.

Hepatic glucuronidation is one pathway involved in the metabolism of some of these compounds and glucuronyl transferase deficiency and therefore more inefficient glucuronide conjugation may be part of the explanation for the apparent sensitivity of cats to pyrethroids, i.e. as they have slower excretion of and therefore more prolonged exposure to accumulating metabolites.

Oral exposure

Oral exposure should be treated by gastrointestinal decontamination if appropriate, including activated charcoal if patient compliance allows. Pyrethrins and pyrethroids are highly fat soluble and low fat foods should therefore be fed in the short-term to reduce further absorption.

Clinical signs

Clinical signs usually develop within a few hours of exposure but can be more delayed. Minor and usually self-limiting signs include hyperaesthesia, hypersalivation, ataxia, mydriasis, paw flicking and ear twitching. These signs may be accompanied by other non-specific signs such as lethargy or transient vomiting and diarrhoea. Severe neurotoxicity resulting from excessive exposure may result in marked depression, ataxia, potentially violent muscle tremors, seizures and death. Protracted gastrointestinal signs may also occur.

Treatment

No specific antidote and management is as above under 'Initial stabilisation – treatment of seizures and muscle tremors'
Topical decontamination (mild detergent + lukewarm water)
Methocarbamol

It is important to check blood glucose concentration in any animal presenting with central neurological signs. Likewise excluding sodium and calcium abnormalities in particular may be appropriate according to the patient's history.
Hyperlactataemia may be present and is most likely to be due to extreme muscle activity (relative oxygen deficiency) rather than hypoperfusion (absolute oxygen deficiency).
A minimum emergency database should be performed at the appropriate time.

Active cooling may be needed initially but bear in mind that temperature will fall with control of signs, washing and sedation/general anaesthesia – it does not usually take much to make a cat hypothermic!

External stimulation should be kept to a minimum (e.g. cotton wool balls/swabs in the ears, dim lighting, minimise noise and passage of personnel). Fluid therapy and appropriate nursing measures should be instituted throughout.

Pyrethrins and pyrethroids are highly fat soluble and there is increasing evidence, both published and anecdotal, that intravenous lipid emulsion (e.g. Intralipid®) therapy has a beneficial role to play in treating these patients. The prognosis for this type of poisoning with standard treatment is reasonable and some would argue that the use of ILE at this time may therefore be best reserved for cases where either euthanasia on financial grounds seems increasingly likely, i.e. due to on-going costs associated with standard treatment, or where clinical signs are (very) severe. ILE therapy is generally considered to be safe with little risk but there are potential adverse effects and as such a risk-benefit assessment is always indicated for what is still considered an 'experimental' treatment. The author has a special interest in ILE therapy and takes a more liberal view to its use in pyrethrin/pyrethroid toxicity but would not recommend its use for example in mild cases expected to be self-limiting with little need of any kind of medical therapy.

Prognosis

The prognosis for full recovery is reasonable despite severe poisoning in animals receiving early and appropriately aggressive intervention; neurotoxicity is fully reversible. In severe cases clinical signs may take 72 hours or more to resolve.

Avermectins and Milbemycins (Macrocyclic lactones)

The macrocyclic lactones (macrolides) include 2 groups, avermectins and milbemycins:

- Avermectins include ivermectin and selamectin
- Milbemycins include moxidectin and milbemycin

These structurally similar compounds are derived from natural compounds produced by soil-dwelling fungi from the genus *Streptomyces.*

Sources

Macrocyclic lactones (MLs) are parasiticides able to kill a wide range of arthropods and nematodes. They are used in many species and found in a wide variety of parasiticide products including some oral and topical preparations used in companion animals. Dogs and cats may also be exposed to large animal products either accidentally or by intentional administration. Many formulations intended for large animals are concentrated so it is easy for accidental overdoses to occur. Many cases of ivermectin poisoning in dogs occur from the ingestion of equine products (usually spilled or dropped) or ingestion of manure from treated horses.

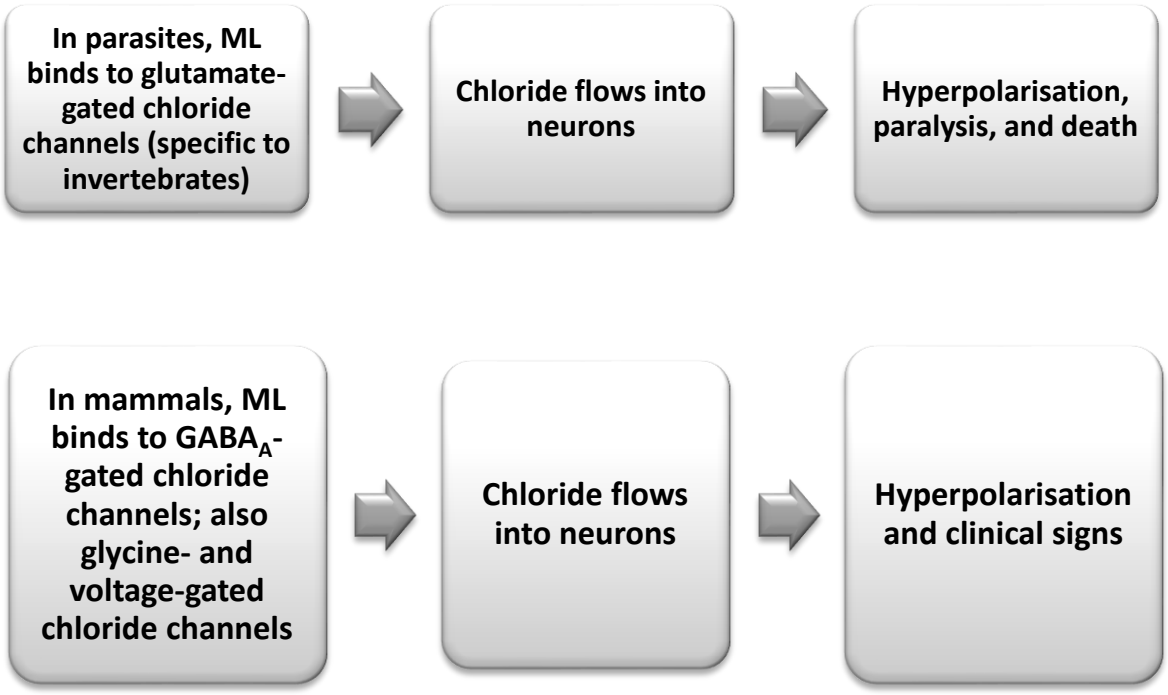
Toxic dose, Toxicokinetics, Mechanism of toxicity

Reported toxic doses in dogs and cats following ORAL exposure:

Macrocyclic lactone	**Acute toxic dose (mg/kg) following oral exposure**		
	Normal dogs	**ML-sensitive dogs**	**Cats**
Moxidectin	1.9-2.8	1.0	1.0
Selamectin	None found	5.0	None found
Ivermectin	0.2-2.5	0.1-0.4	None found

One main mechanism by which the MLs exert their effect is by binding ligand-gated chloride channels. Binding of glutamate-gated chloride channels, which are specific to invertebrates, causes influx of chloride ions into the parasite neurons leading to hyperpolarization, paralysis, and death.

In mammals, MLs bind to gamma-aminobutyric acid type A–gated chloride channels ($GABA_A$ receptors). GABA is the primary inhibitory neurotransmitter in the brain, and postsynaptic binding of GABA to its receptors serves to modulate firing of excitatory neurons, such as glutamatergic neurons. MLs are believed to bind $GABA_A$ receptors at sites different than those where GABA, benzodiazepines or barbiturates bind. Because $GABA_A$ receptors are only present in the CNS, binding of MLs is prevented by the blood-brain barrier (BBB). However, in overdoses, enough ML permeates the BBB that binding to $GABA_A$ receptors, as well as to glycine- and voltage-gated chloride channels, occurs. Subsequent chloride influx causes hyperpolarisation and decreased firing of the excitatory neurons that express these chloride receptors and channels, leading to clinical signs.



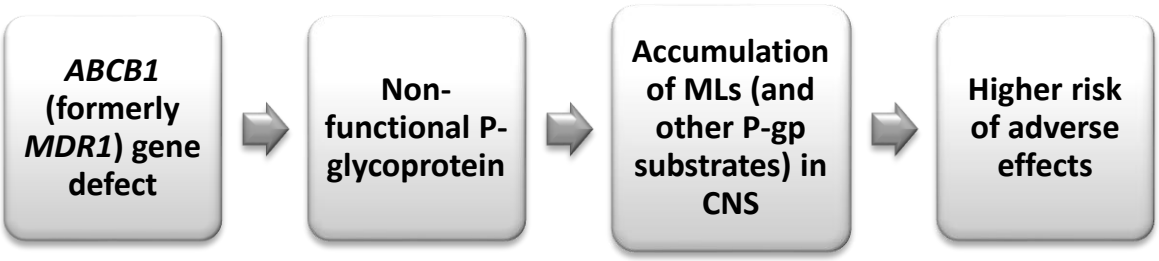
In general, the MLs have relatively fast oral absorption. They also are all highly fat soluble, have a large volume of distribution, and accumulate in fat tissue resulting in a long elimination half-life. Specific information about metabolism and amounts of drug or metabolites eliminated in bile and urine in the dog or cat is lacking at this time. Enterohepatic circulation probably occurs for at least some MLs. Bear in mind that differences in product formulation can alter pharmacokinetic parameters significantly even for the same agent.

Role of P-Glycoprotein:

Permeability glycoprotein (P-gp) is a transmembrane efflux protein that influences the pharmacokinetics of many of its substrates, including MLs, by actively transporting absorbed substrates back across a variety of cell membranes in the body. It essentially has a protective function because it limits entry of substrates into internal compartments. P-gp is a component of the BBB and is important in limiting the entry of MLs and other xenobiotics into the CNS.

Dogs of certain breeds and mixtures of those breeds have a defect in the *ABCB1* gene (formerly *MDR1* gene) that codes for P-gp and this defect results in production of non-functional P-gp. A lack of functional P-gp leads to accumulation of the MLs in the central nervous system (CNS) and a higher risk of adverse effects when exposed. Lack of functional P-gp may also affect ML pharmacokinetics in other ways that are as yet poorly studied.

The *ABCB1* gene mutation is typically seen in herding type breeds, primarily collies as well as Shetland sheepdogs and Australian shepherds; in addition, it has been detected in longhaired whippets, old English sheepdogs, silken windhounds, white Swiss shepherds, German shepherds, and some mixes of these breeds. Dogs can be easily tested for the gene defect.



Clinical signs

Signs of intoxication with MLs generally are related to the central nervous system secondary to enhanced neuronal inhibition and onset is typically within a few (e.g. eight) hours; can take as little as 2 hours or as long as 12 hours. Neurological depression, ataxia, mydriasis, blindness, tremors, and hypersalivation all may be seen and, as signs progress, an animal may become comatose. Confusion, agitation, hyperaesthesia and hyperthermia are possible and seizures may also occur. The blindness is typically temporary and has been associated with retinal oedema and electroretinogram abnormalities in the case of ivermectin.

The signs seen are similar in both dogs and cats for all the MLs. Depending on the dose and the breed involved and due to the long half-life of these agents, toxicosis may persist for days to weeks.

Treatment

There are no specific antidotes for ML toxicosis. Appropriate decontamination and good supportive care are the cornerstones of treatment. Some patients need to be hospitalised for several days or longer, so it is important that animal owners are advised up front regarding this possibility. However, with commitment to treatment, it is possible for even severely affected animals to make a complete recovery.

Gastrointestinal decontamination:

Gastric emptying is indicated if oral exposure was within an appropriate timeframe (e.g. 2 hours). Inducing emesis may be considered if the animal is asymptomatic, otherwise consider gastric lavage. Although the efficacy of activated charcoal in treating overdoses of MLs has not been established an initial dose is likely to be of benefit if given within the first 4 hours of ingestion given what is known regarding the absorption rate of MLs. Since there is evidence that MLs are enterohepatically circulated, it is reasonable to consider repeated doses of activated charcoal in small animal patients regardless of the route of exposure.

Symptomatic and supportive care:

Fluid therapy, good nursing care of the recumbent animal, and thermoregulation are essential for these patients. If respiratory depression develops, patients may require oxygen supplementation, intubation, and positive pressure ventilation. Nutritional support may also be needed. If bradycardia develops, a low dose of atropine or glycopyrrolate may be given.

Treatment of tremors or seizures resulting from ML toxicosis is a controversial topic, with the uncertainty of which drugs to use being the main question and the debate centring on both the binding of different agents to the GABA receptor, where on this receptor each agent binds, and how binding of one agent versus another may affect ML-induced toxicity.

A number of resources suggest that benzodiazepines and perhaps barbiturates should not be used in the treatment of ML toxicosis due to the potential to worsen clinical signs. But this recommendation is based on limited theoretical information without a supportive clinical evidence base. [While benzodiazepines such as diazepam can potentiate GABAergic effects so can barbiturates and propofol which both bind $GABA_A$ receptors albeit at different sites than benzodiazepines and MLs. The present state of knowledge is that there are several different binding sites on $GABA_A$ receptors each of which binds different types of xenobiotics. The different binding sites interact allosterically with binding of a compound to one site influencing the likelihood of different compounds binding to other sites — all of which then influence opening of the channel in the receptor and subsequent chloride influx. Assessment of allosteric relationships in the $GABA_A$ receptor can be very challenging and the relationships between MLs and drugs that bind $GABA_A$ receptors have not been well investigated. Until these allosteric relationships are better established…] it is the author's opinion that diazepam, barbiturates, or propfolol may be cautiously used to attempt to control tremors or seizures.

Intravenous lipid emulsion:

Intravenous lipid emulsion therapy has been suggested to be a treatment that may shorten the duration of clinical signs of ML toxicosis and there are a small number of individual case reports that may support this notion. All of the MLs are lipophilic so lipid therapy is potentially beneficial in treating toxicity from any of the avermectins or milbemycins. Moxidectin is likely the best candidate for this therapy due to its very high lipid solubility. The effectiveness and safety of this treatment in reducing the duration of clinical signs or improving outcome with acute toxicosis in clinical patients has not been proven in human or veterinary patients but clinically significant adverse effects are currently considered to be very uncommon with ILE therapy and the risk-benefit assessment seems to fall on the side of potentially significant benefit with comparatively little risk. As mentioned above, some cases of macrolide poisoning can persist for lengthy periods of time and any therapy that may potentially minimise the chances of severe intoxication seems worthy of consideration. As such ILE therapy is recommended in patients with severe signs (e.g. severe stupor/coma, seizures) of ML intoxication.

Assuming ILE is effective in the treatment of ML toxicosis it theoretically may be less effective in dogs with a lack of functional P-gp, e.g. these dogs may have higher CNS levels of the ML and/or impaired elimination of the ML from the CNS due to non-functional P-gp.

Prognosis

The prognosis may be guarded to good depending on the exposure dose and agent involved. Severely affected dogs may require long-term care, which may be a financial burden for some owners. Depending on the dose and half-life of agent involved, recovery can take days to weeks. After recovery, long-term sequelae are not expected. Sedation and blindness seem to the longest lasting signs, but even blindness is not expected to be permanent as most dogs seem to recover visual ability.

Chocolate

A 3-year old Shih Tzu has eaten some dark chocolate 2 hours before presentation. On presentation he appears restless and excitable and on cardiovascular examination he has tachycardia above 200 bpm with peripheral pulse deficits; he vomited during the initial examination. What should you do?

A. Administer aggressive isotonic crystalloid fluid therapy as he must be in hypovolaemic shock
B. Perform an ECG as chocolate toxicity can cause dysrhythmias which must be characterised before treatment can be considered
C. Induce emesis

The correct answer is B. The dog's tachycardia with pulse deficits is most likely related to a theobromine-induced dysrhythmia and aggressive fluid therapy is not indicated in such cases. Induction of emesis is not necessary as the dog is already vomiting and may also not be advisable as he is restless and excitable which may increase the risk of aspiration.

Theobromine is a methylxanthine-derived alkaloid occurring naturally in cacao beans and found in chocolate, cocoa powder and other products produced from these beans. In addition chocolate contains a lesser amount of caffeine, also a methylxanthine.

The concentration of theobromine varies in different sources: plain (dark) chocolate and cooking chocolate generally containing significantly more than milk chocolate. The theobromine content of white chocolate is considerably lower. Cocoa beans, cocoa powder and cocoa shell mulches contain the highest concentrations of theobromine. The literature contains reports of death in dogs following consumption of chocolate, cocoa powder, cacao bean shells and cocoa bean mulch.

It is also important to remember that the theobromine concentration can vary even within types, e.g. the milk chocolate in one product could contain more or less theobromine than the milk chocolate in another product. Furthermore chocolate products may contain other toxic components such as raisins, peanuts, coffee beans or xylitol.

Toxic dose, Toxicokinetics

Fatal doses of theobromine in dogs are reported to be in the range of 90-300 mg/kg and in cats 80-200 mg/kg. It may be difficult to actually establish theobromine exposure and calculations are usually done on the basis of weight of chocolate product rather than theobromine itself. One recommendation is to perform gastrointestinal decontamination if the patient has ingested:

- More than 9 grams of milk chocolate/kg
- More than 1.25 grams of dark chocolate/kg

The following online interactive chart may prove very helpful in decision-making with these cases; the source of the information is quoted as the ASPCA but note that the author has not meticulously validated its accuracy using other references (!):

http://ngm.nationalgeographic.com/2007/10/pets/chocolate-chart-interactive

Absorption of theobromine from the gastrointestinal tract is relatively slower in dogs compared to people with complete absorption potentially taking up to 10 hours. Metabolism is primarily hepatic and enterohepatic circulation occurs. Excretion is considerably slower than in people. As always, check with poisons information resources for the most recent information.

Mechanism of toxicity

Methylxanthines inhibit cyclic nucleotide phosphodiesterases and also act as adenosine receptor antagonists. As with other methylxanthines, theobromine (and caffeine) causes central nervous system stimulation with consequent cardiac and respiratory effects. It directly stimulates the myocardium and skeletal muscle causing increased contractility (by inhibiting cellular calcium reuptake) and competitively inhibits cerebral benzodiazepine receptors. Theobromine also causes smooth muscle relaxation, especially of the bronchi, and renal diuresis.

Clinical signs

Clinical signs usually develop within 24 hours of ingestion and typically much sooner – within 4 hours. Signs may persist for 48-72 hours in some cases. Commonly reported clinical signs include vomiting, abdominal discomfort, restlessness, excitability and hyperactivity, ataxia, tachycardia, and tachypnoea or panting. In more severe cases muscle rigidity, muscle tremors, hyperthermia, seizures and dysrhythmias have been reported. Urinary incontinence, polyuria and polydipsia may also occur. Severe seizures and/or cardiovascular compromise are typically reported in fatal cases.

An **emergency database** including electrocardiogram is recommended.

Treatment

Routine GID is indicated in appropriate cases. As theobromine is absorbed slowly in dogs induction of emesis may be appropriate even after a significant delay; however it is best avoided in animals that are very hyperactive/showing neurological compromise. Theobromine undergoes enterohepatic circulation so repeated use of charcoal may enhance elimination. There is no specific antidote for theobromine poisoning and therapy is otherwise symptomatic and supportive. This may include intravenous fluid therapy, anti-emetic administration, sedation if excitability is excessive, and routine treatment of seizures.

Anti-dysrhythmic therapy may also be indicated in some cases. Severe or prolonged sinus tachycardia may be treated with an injectable beta-blocker if available. Lidocaine should be used if clinically significant ventricular tachycardia develops and may also be tried if a supraventricular dysrhythmia is present and more traditional agents for SVT such as an injectable calcium channel blocker are not available.

Prognosis

Prognosis is generally good with appropriate treatment but may be worse for animals showing marked cardiovascular or neurological signs at presentation.

(Appendix 1) Inducing Emesis in Cats

This is a blog post written by the author in July 2014.

Cats do not tend to ingest poisons as often as dogs do, this we know, and therefore the scenario in which one may be considering inducing emesis in a cat is encountered less often. That said, the Veterinary Poisons Information Service (VPIS), based in the UK, gets more or less one telephone enquiry a day about a cat that has ingested a toxin (personal communication, 2014) so it is not totally unheard of! I am going to skip some of the other talking points about gastrointestinal decontamination, especially in cats, here and just consider the circumstance in which it has been decided to induce emesis in a cat. What are the options?

Before proceeding I would like to state two points in particular outright:

1. We need to set everything that follows in the context of evidence-based medicine principles and critique. It is clear that we are really scratching around here for evidence and such things as a number of prospective randomised controlled trials followed by systematic review/meta-analysis are extremely unlikely to ever be forthcoming.
2. By referencing experimental studies I do so to convey the available information without condoning them. This is not the place to have that debate but one point that must be borne in mind, and relates to point 1. above, is that the translatability of experimental studies on small populations of cats to decision-making for individual clinical patients needs to be kept in the forefront of our minds. Admittedly cats that have poisoned themselves and in whom emesis is being considered are typically healthy but nevertheless the point is salient.

Alpha$_2$-adrenergics

For many years it has been said that xylazine is the agent of choice for inducing emesis in cats. I have never personally used it but I have met people who have and they seem anecdotally to support the notion that it is effective There are some experimental reports looking at xylazine-induced emesis (e.g. Lucot, Crampton, 1986). Colby et al (1981) found a dose of xylazine of 0.66 mg/kg injected intramuscularly in normal cats caused vomiting in 20/21 cases; other doses have been reported too (e.g. 0.4-0.5 mg/kg). I also found the Moye, Pailet, Smith (1973) paper listed below but I cannot access it to see just how 'clinical' it really is. There are a number of papers you can find that study the anti-emetic effects of various agents or methods of neuroinhibition on cats that have been or are scheduled to be treated with xylazine to induce emesis. For example see Chiu-Ming Ho et al, 2001; Kolahian, Jarolmasjed, 2010; Kolahian, Jarolmasjed, 2012; there are quite a few others!

But it is not just xylazine. Other alpha$_2$-adrenergic agonists are reported to cause vomiting in cats. You can find papers where the potential for medetomidine and dexmedetomidine to cause emesis in cats is discussed/studied. For example see Santos et al (2011) in which dexmedetomidine was used at 40 µg/kg intramuscularly; there are other papers including reference to using medetomidine at 20 µg/kg.

Clearly the main clinical use of alpha$_2$-adrenergic agonists is as sedative agents with emesis typically occurring if it does as an unwanted side-effect. A sedate cat that vomits is at increased risk of aspiration, and moreover these agents can also cause potentially profound dose-dependent cardiorespiratory compromise. I am sure it must be quite distressing to be vomiting and nauseous when also in a state of sedation! So their use is far from ideal but anecdotally relatively reliable at inducing emesis and reversal agents do exist. Atipamezole is used for (dex)medetomidine. Yohimbine has traditionally been recommended for xylazine but availability is likely to be very limited nowadays; it is suggested that atipamezole may also reverse xylazine's effects but I am not sure whether there is any substantive evidence.

Xylazine is I think still used in larger species but with the increase in small animal-only practices worldwide the availability of xylazine is something we need to consider. I know some practices that stock it solely for inducing emesis in cats; I believe an open vial must be discarded after 28 days and in most cases this will mean discarding the vial after use in only one cat. Otherwise (dex)medetomidine is the option and widely available.

Apomorphine

But the question that always comes up is what about apomorphine – can we use it in cats? Is there evidence that it works for inducing emesis? What are the potential risks? What is the risk-benefit analysis and moreover how does it compare to using the agents mentioned above?

For as long as I can remember resources that I have come across have said that apomorphine should not be used in cats.

Often they do not explain why or offer substantive references; however some reasons that I have occasionally read are that apomorphine is associated with more significant side-effects in cats, especially cardiovascular depression or sedation, or that it is ineffective. I spent some time seeing what I could find in the literature.

In Batchelor at al. (2013) it says “certain important differences exist between dogs, cats…For example, D2 dopamine receptors in the AP [area postrema, chemoreceptive area] are much less important in cats than in dogs, explaining the comparative resistance to apomorphine-induced vomiting in cats. In contrast, α2 adrenergic receptors are important in the areas of the cat brainstem controlling vomiting, explaining why the α2 agonist xylazine is an effective emetic agent in cats”. Unfortunately I cannot access the reference they cite in this paper to substantiate the idea that cats are comparatively resistant to apomorphine-induced vomiting.

In Graf et al (1979) it says in the abstract “among xylazine, ipecacuanha solution, apomorphine and copper sulphate, xylazine was the most reliable emetic (1 mg/kg body weight s/c). Apomorphine was unsuitable for cats in a dose of 10-20 mg because it produced excitement and seldom vomiting”. This is obviously a considerably higher dose than we would use clinically; a typical clinical dose range in dogs is 40-100 µg/kg but you will not find a dose range for cats listed in any/many resources. You can also come across papers where emesis is reported to have been induced in cats using apomorphine as part of experimental research; for example see Ognean (2000) or Boyd (1953) – in the latter it says in the abstract “an account of experiments which indicated that, in amounts corresponding to the usual human therapeutic doses, none of the antihistaminics tested-three diphenhydramine derivatives and prornethazine hydrochloride, methapyrilene hydrochloride, and methapyrilene-8-chlorotheophyllinate-prevented apomorphine-induced emesis in dogs and cats”. Unfortunately I cannot access these papers to review them especially with respect to what doses were used.

Apomorphine administered intravenously at a dose range which included at the very bottom end doses used clinically but also very high doses (10-750 µg/kg) reportedly produced a dose-dependent fall in mean systemic arterial blood pressure in cats; this was accompanied by marked bradycardia at the higher doses (500-750 µg/kg)(Ramirez, Enero, 1980). Similar findings were also reported in a later study (De Meyer, Buylaert, Bogaert, 1982) and there are others. However we must note that apomorphine administered intravenously at actually lower doses (1.25-20 µg/kg) than we would use clinically reportedly caused a dose-dependent decrease in blood pressure in dogs as well (Bogaert, Buylaert, Willems, 1978). Of course the relevance of such experimental studies in anaesthetised animals to conscious clinical patients is questionable; while both cohorts may typically be healthy, anaesthesia and anaesthetic drugs are clearly confounders to any reliable comparison before we even get into details about the animals being comparable etc.

At (much) higher doses that we would use clinically apomorphine has been reported to cause motor activity, including limb flicking for example, in experimental cats that may be due to a central dopamino-mimetic action of the drug.

For example in one study doses of between 100-2000 µg/kg were used and “apomorphine elicited limb flicking, dose-dependent hypermotility and increase in olfactory behavior, the last two reactions with stereotypy characteristics. The animals appeared as if being scared, hyperreacting to sudden stimuli and showing total indifference to the surrounding environment”(Motles, Martinez, Concha et al, 1989). Clearly the bottom end of this dose range is 5-10 times the starting doses we may use clinically. There are other similar papers reportedly showing similar things, i.e. motor activity and behavioural changes, but again at high doses sometimes given by routes we would not use clinically.

Naloxone is said to be able to reverse adverse effects of apomorphine without impairing its emetic effect. Again I am not aware of and have not had chance to investigate what evidence if any there is for this assertion but I am pretty sure it is based on the theory behind the mechanisms by which apomorphine induces emesis versus causes other side-effects (dopamine versus opiate effects etc.).

I should also mention at this point that I have again never personally tried this but soda crystals may be considered in cats. You will also find some people suggesting that hydrogen peroxide can be used; I personally do not like this idea in cats or dogs for that matter and again have never done it. I am not going to say any more about these substances here as this is already a long blog!

So what's the bottom line?

Well, it is a good question. Clearly we would love for all this to be evaluated 'properly' and according to robust evidence-based medicine principles in clinical patients…but we must not hold our breaths! I have in the past used apomorphine in 3 cats at a dose of 20 µg/kg and emesis occurred in 2 of these cats. According to some of the material above, this makes little sense as this dose is half the dose I usually start with in dogs and cats are meant to be more resistant to apomorphine! The reason I chose this 'lower than in dogs' dose was due to the concerns that I had come across in resources about using apomorphine in cats. I have seen some cases in which medetomidine was used as 10-20 µg/kg and emesis occurred; but I have also seen cats become very sedated with nausea but no emesis. I must re-emphasise that we are talking about very small numbers of cats here.

Based on this present round of research I think I will be tempted to give the next cat in which I want to induce emesis apomorphine at an initial dose of 40 µg/kg and then decision make from there based on what occurs. Above there are some references to cats maybe being more resistant to the emetic effects of apomorphine than dogs but thus far I am struggling to find evidence of increased susceptibility to adverse effects, especially in the dose range that we would likely use clinically. While I continue to mull this over I would love to hear your experiences/thoughts/suggestions…

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