**Supporting the intoxicated veterinary patient (part 2): Toxicants affecting the neurological and cardiovascular systems.**

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KEY LEARNING OUTCOMES

After reading this article, you should understand:

* ▢ The pathophysiology behind common neurological and cardiovascular toxicants
* ▢ The structured approach to neurologically and cardiovascularly intoxicated patients and their management
* ▢ The indications for common antidotes and lipid emulsion therapy in both cardiovascular and neurological intoxications

 A previous article has discussed the basic approach to decontamination of the asymptomatic patient exposed to a toxicant. This aim of this article is to focus on toxins which affect the neurological and cardiovascular systems. Severe derangements in these two systems are life threatening and it is important to know how to stabilise and support these consequences of intoxication. In this article we will discuss the principles of management and specific toxicants that affect these systems.

**Neuro-excitation and neuro-inhibition in neurotoxicants**

Neurotoxins can affect the central or peripheral nervous system (CNS and PNS) directly or indirectly. Indirect consequences occur when the primary target is neither the CNS nor PNS, but another system within the body. Examples of indirect neurological effects of intoxicants include; hepatotoxicity causing hepatic encephalopathy or hypoglycaemia (e.g. *amanita* mushroom intoxication), insulin release and hypoglycaemia (e.g. xylitol), severe hypo/hypertension altering mental status (e.g. β blocker and calcium channel blocker toxicity) or metabolic shock (e.g. in methaemoglobinemia). The onset of action and progression in direct neurotoxicities are normally very rapid. However, this is not always the case, with lead and macadamia nut ingestion being examples of direct neurotoxicants that can cause a more delayed onset of clinical signs. 1 Neurological signs of intoxications are often classified as predominantly excitatory or inhibitory. Excitatory effects on the CNS include hyperexcitability and seizures and on the PNS include muscle tremors, fasciculations, and occasionally ataxia. Inhibitory effects on the CNS include obtundation, stupor and coma and on the PNS include weakness, flaccid paralysis and respiratory depression when severe. Some toxins can cause either hyperexcitability or inhibition depending on the dose (e.g. amitraz) or can progress from excitatory to inhibitory over time. Alternatively, patients might transition between a hyperexcitable and inhibited state (e.g. marijuana toxicity), depending on the degree of environmental stimulation. Table 1 details the neurological clinical signs associated with common intoxications.

***Initial management of neurotoxicants***

*Major body system assessment-* Because the clinical signs of neurotoxicants can progress rapidly, prompt evaluation of the patient is necessary, even in non-symptomatic patients. In a symptomatic patient (seizing, tremoring or obtunded), the initial exam might need to be delayed until an intravenous catheter is placed. This will allow timely control of excitatory signs and help facilitate the delivery of anaesthetic agents if endotracheal intubation is required. Collection of baseline bloods from the intravenous catheter prior to treatments should be performed because some medications (diazepam or activated charcoal) can interfere with point of care tests (e.g. ethylene glycol snap test). 2

Once the initial signs of the intoxication are managed, a physical examination can follow. With the cardiovascular system also commonly affected by neurotoxicants, a blood pressure and ECG should be included in the initial evaluation. Mucous membranes should be carefully examined as certain neurotoxicities will cause alterations in colour such as cyanide (cyanosis) and carbon monoxide (cherry red). Respiratory patterns (and where possible, venous or arterial blood gas samples) should be analysed because neuro-inhibited patients may hypo-ventilate. There are also certain neuro-toxicants that can cause respiratory paralysis (nicotine, acetylcholinesterase inhibitors, cyanobacteria).3 All patients (whether inhibited or hyperexcitable) are predisposed to aspiration events; thoracic auscultation and point of care ultrasound should be repeatedly performed (Figure 1). In both inhibited and hyperexcitable patients, body temperature may be altered (hypothermia and hyperthermia respectively).

*Stabilisation of neurological signs-* In the actively seizing patient diazepam or midazolam are the first line therapy (Table 2). In patients refractory to IV benzodiazepines, propofol can be used to control the visible muscular acivity but an anti-epileptic drug such as phenobarbitone or levetiracetam must be used concurrently to control the actual seizure activity underlying. Some authorities advocate the use of levetiracetam over phenobarbitone to limit the degree of sedation, however in some cases this sedation is beneficial. A constant rate infusion of benzodiazepines can also be added in addition to infusions of propofol in severe cases. Benzodiazepines may occasionally cause disinhibition and exacerbate hyperaesthesia. It may then be necessary to administer additional sedation until these effects subside. There are certain situations where benzodiazepines should be avoided (serotonin syndrome and amphetamine intoxication). If the patient is tremoring rather than seizing, methocarbamol will be more appropriate. Guaifenesin can be used where IV methocarbamol is not available, and oral methocarbamol tablets can be crushed, dissolved and administered per rectum. Methocarbamol can be combined with diazepam for additional muscle relaxation effects. To control CNS excitation, tranquilizers such as acepromazine (0.005-1mg/kg IV) may be required. These can be particularly useful in cases of methylxanthine, marijuana and amphetamine toxicity. Consideration of haemodynamic status when choosing a sedative to control CNS excitation is important. Combining low doses of acepromazine (0.005mg/kg) and butorphanol (0.1-0.2mg/kg IV) or even the addition of a butorphanol CRI can be useful.

 Patients with seizures or tremors may become hyper-thermic. When the rectal temperature is ≥40°C (104°F), the patient should be aggressively cooled. This is best achieved using convective cooling (by wetting the skin and coat with cool water and using an electric fan, towels should not be applied as they act as blankets preventing evaporative loss). Active cooling should stop when a rectal temperature of 39.7°C (103.5°F) is reached to avoid hypothermia as patients may also have poor thermoregulation. More aggressive methods of active cooling may be necessary in cases suffering from malignant hyperthermia (e.g. hop ingestion). Depressed patients are more likely to be hypothermic and will require active warming.

*Stabilisation of major body system concerns*- Intravenous fluid therapy of isotonic, balanced crystalloids (compound sodium lactate, Normosol R, Plasma-lyte®) are good choices in most cases for resuscitative and ongoing fluid requirements. The exception will be in salt toxicity. Most of the time salt toxicity will be acute, meaning rapid reduction of blood sodium levels can and should be initiated. Paintball toxicity is suspected to be due to free water losses rather than a salt gain per say and fluid therapy with a low sodium content (0.45% NaCl + 2.5% dextrose) or 5% dextrose in water to correct the free water deficit will be needed. Estimation of free water deficit (Free water deficit in litres = [(Patient Na+/Normal Na+)-1] x (0.6 x kg BW) will calculate the volume of 5% dextrose that can be given over a defined period (decreasing Na+ at 1-2mmol/L/hr) if the animal is not drinking.

4 Lower sodium containing fluids will also be needed in cases with salt gain (table salt ingestion) however these cases are at risk of fluid overload because of their total body sodium increase and should be monitored for this closely (increase in body weight, respiratory rate, serous nasal discharge, subcutaneous oedema etc). When the chronicity of hypernatraemia is unknown, a fluid with a higher sodium concentration (e.g. 0.9% NaCl) is needed to minimise the risk of cerebral oedema (avoiding a drop of Na+ > 0.5mmol/L/hr). Ongoing losses will be increased in patients receiving mannitol or cathartics as part of their management and ongoing fluid rates will need to include these losses. Fluid therapy is particularly important in neurotoxicants known to cause renal injury (e.g. lead) and also in cases suffering rhabdomyolysis with pigmenturia from severe excitatory signs as myoglobinuria could cause acute kidney injury.

Oxygen therapy could be required in cases suffering from respiratory depression, aspiratory pneumonia/pneumonitis or non-cardiogenic pulmonary oedema (seen with severe seizures). Specific toxicants resulting in tissue hypoxia and neurological signs include carbon monoxide, and cyanide. Methods of oxygen supplementation used will depend on the severity of hypoxaemia however, intranasal cannulae should be avoided if there are concerns over raised intracranial pressure (to minimise the risk of sneezing). A severely depressed patient with a poor gag reflex will need airway protection using a cuffed endotracheal tube. This might also be the case if the depression is iatrogenic during seizure management.

Intravenous lipid emulsion (ILE) can be used in most cases because of its wide safety margin. It has been used in veterinary patients intoxicated with; macrocyclic lactones, permethrins, local anaesthetics, serotonergic drugs and muscle relaxants (baclofen). 5-8

Mannitol or hypertonic saline should be used in cases when raised intracranial pressure is suspected (Cushing’s reflex, deteriorating mental status) and cerebral oedema is highly likely, for example in bromethalin, lead and water intoxication.9

Certain toxicities (ethanol, ethylene glycol) can result in a severe metabolic acidosis. Sodium bicarbonate can be considered when the venous blood pH is < 7.1, particularly if renal function is impaired (Table 2). Bicarbonate therapy has also been advocated to alkalinise urine in an effort to ion trap certain agents and aid with removal (e.g. phenobarbitone, salicylates, cyclic antidepressants). Risks with this therapy in this setting include paradoxical central acidosis and cerebral vasodilation impairing autoregulation of blood flow to the brain.

# *Selecting antidotes*- Available antidotes include atropine, which is indicated for toxins exacerbating muscarinic signs (acetylcholinesterase inhibitors) and pralidoxime (2-PAM) which is used to reverse the nicotinic signs in organophosphate poisoning (but is contraindicated in carbamate toxicity). Chelation agents (succimer) are available for lead toxicity however these are not indicated until the source of lead is removed from the gastrointestinal tract. Inhibition of alcohol dehydrogenase using ethanol or 4-methyl-1 H-pyrazol (fomepizole) is extremely unlikely to be beneficial in ethylene glycol toxicity unless performed within 3-4 hours of ingestion.10 The lack of availability of fomepizole in many countries including the U.K. means that although this is the preferred antidote, ethanol would need to be used. In certain neurotoxicities, other supplements can be considered. Lead toxicity might respond to thiamine and zinc supplementation.

*Decontamination*- Because neuro-intoxications often present very shortly after exposure, decontamination through emesis induction can be an important part of therapy. Generally, this is suggested to be performed within 2 hours of ingestion (see Article 1), but this depends on many factors including the toxicant being considered. Chocolate ingestion can cause delayed gastric emptying so can be recovered by emesis up to 12 hours after ingestion. Emesis should not be attempted in overtly clinical patients (moderate to severe tremors, seizing or reduced mentation) as there is a risk of aspiration. Moreover, emesis can result in raised intracranial pressure. Inducing emesis can also worsen clinical signs in neurotoxicities that cause hyperaesthesia, tremors or muscle spasms (e.g. strychnine, cyclic antidepressants). If the patient is overtly clinical (profound CNS depression or neuroexcitation), vomiting has not already occurred and recent ingestion of a lethal dose of toxicant is suspected, gastric lavage is indicated. Colonic lavage can be considered in the per acute stages of management in certain cases (organophosphates and carbamates) because they course rapidly through the gastro-intestinal tract. Certain neuro-toxicants may not bind to charcoal or charcoal is contraindicated and these include salt (NaCl), xylitol, alcohols (methanol, ethanol, ethylene glycol), petroleum products, strong acids or alkalis and dissociable salts (lithium). 1 Some neurotoxins may be absorbed via dermal exposure (e.g. pyrethroids and anticholinesterases) and the animal will need to be clipped and washed with a mild detergent to remove these agents.

*Laboratory evaluation*- Baseline bloods will allow monitoring of potential hepatic, renal and haematological consequences of intoxication. When the toxicant is known, a more targeted choice of blood analysis can be performed. For example, monitoring a renal profile when ibuprofen toxicity is suspected, or a liver profile in xylitol toxicity. Venous blood gas analysis can reveal derangements indicative of neurointoxications. An increased anion gap, normo-chloraemic, metabolic acidosis can be seen in acetaminophen, salicylate, cyanide, methanol, ethylene glycol and cyanide toxicities. 11 A metabolic acidosis is common in cases of metaldehyde toxicity and hyperlactataemia can be seen in cyanide and ethylene glycol toxicity. 9, 12 The elevated lactate in ethylene glycol occurs when analysers (e.g. Radiometer ABL) that measure L-lactate cross react with ethylene glycol metabolites. Some analysers will not cross react with the metabolites (i-STAT) and so a ‘lactate gap’ can be seen between the two methods. 13 An elevated venous oxygen saturation (>70%) or a decrease in arterial-venous oxygen saturation difference could also indicate cyanide toxicity. 12 Co-oximetry on blood gas analysers will allow carbon monoxide levels to be evaluated. Ethylene glycol toxicity will cause an increase in the osmolar gap (osmolar gap = measured - calculated osmolarity) for up to 18 hours after ingestion however, osmometry is rarely available to use this. Plasma sodium concentration will be elevated in salt intoxication and paintball ingestion and reduced in water intoxication and should be part of the initial evaluation. Other parameters that should be evaluated are glucose and ionised calcium as these could be altered in ethylene glycol toxicity (hyperglycaemia and hypocalcaemia) and xylitol (hypoglycaemia) ingestion. 9

A point of care blood test for ethylene glycol is available (Kacey EG Test Strips, Kacey In, Asheveille, NC) but false positives are possible, and it is less reliable in cats. 2 A simple test (although variably reliable) to support ethylene glycol ingestions is positive fluorescence by Wood’s lamp examination of vomitus or urine (up to 6 hours). In addition to this, the urine can be examined for calcium oxalate monohydrate crystalluria which is seen within 3-6 hours of ethylene glycol intoxication. Urine drug test kits available in pharmacies for humans can be used to screen for recreational drug intoxications but need to be interpreted with caution as they are not validated for use in animals. Unfortunately, there are few antidotes in veterinary toxicology meaning the value in identifying the toxicant is not necessarily in finding an antidote, but more to enable anticipation of other systemic effects and to determine prognosis. Confirming that a toxin is the cause of the clinical signs also means that effort can be saved on surplus diagnostic investigations.

**Common toxicities directly affecting the neurological system:**

***Cannabinoids (Marijuana, cannabidiol and synthetic cannabinoids)***

There are a growing number of sources from which pets can be exposed to cannabinoids. Some include marijuana, cannabidiol (CBD) and synthetic cannabinoids (SCB). Marijuana is the dried preparation form of the leaves and stems of the *Cannabis Sativa* plant. Cannabidiol is a non-psychoactive cannabinoid sold commonly for health benefits (sometimes as an oil) and synthetic cannabinoids are sold for recreational use. 14 The synthetic products are known by many names including; Spice, K2, Black-mamba, Skunk and Zombie. The active cannabinoid in marijuana is 9-tetrahydrocannabinol (THC) which binds a cannabinoid receptor (C1) centrally to cause the inhibition of release of multiple neurotransmitters including acetylcholine, glutamate, GABA, norepinephrine, dopamine and 5-HT). 15 Synthetic cannabinoids will also bind this receptor but with greater affinity and potency. Cannabidiol is non-psychoactive because it does not bind to the C1 receptor. The most common route of exposure of cannabinoids is ingestion and onset of clinical signs is usually seen within 1-2 hours. 15 Clinical signs in marijuana toxicity include ataxia, depression, altered mentation, hypersalivation, mydriasis, nystagmus, bradycardia, hyperaesthesia, urinary incontinence and coma. Because cannabidiol does not bind the C1 cannabinoid receptor, less severe signs are expected with overdose compared to THC containing products. Some of the CBD products can, however, also contain THC (usually in low concentrations) even when not listed as ingredients. 16 Due to the high potency of SCBs for the C1 receptor, more extreme clinical signs than marijuana toxicity are expected, but clinical effects data are limited for veterinary species. Treatment for cannabinoid toxicity is mostly supportive. Fatalities are rare for marijuana and unlikely with cannabidiol; however, based on human reports, they are more likely with synthetic cannabinoids. 15 An awareness of the different types of cannabinoids available is therefore important. Repeat doses of activated charcoal should be given due to enterohepatic circulation in addition to intralipid therapy due to the lipophilicity.

***Pyrethrins***

Pyrethrins and pyrethroids (derivatives of pyrethrins) are insecticides used commonly in veterinary medicine for flea control. The main source of toxicity in clinical practice is when dog flea treatments are applied to cats. Dermal absorption occurs however the majority of bioavailability of the occurs when the agent is groomed off the fur. The toxic effects are elicited through interaction of the agents with voltage-sensitive sodium channels. Clinical signs typically occur within a few minutes however may be delayed up to 72 hours. 12 These signs include tremors, hyperexcitability, hypersalivation, seizures and depression. Decontamination requires bathing in warm water with a mild detergent. Hypersalivation could indicate oral exposure and general gastro-intestinal decontamination guidelines apply. Enterohepatic circulation occurs with some pyrethroids. Treatment is supportive and aimed at controlling tremors and seizures. Intralipid should be used in these cases as we have an evidence base for their benefit. 17

***Tremorgenic mycotoxins***

Decomposing food (commonly bread, vegetables, cheese and nuts) contain multiple different tremorgenic mycotoxins, produced by *Penicillium* fungi. The most common mycotoxins affecting dogs are penitrem A and roquefortine and the mechanism of action is largely unknown but possibly due to inhibition of glycine in inhibitory neurons. 9 Clinical signs of generalised, progressive tremors are typically sudden onset and can resemble a seizure. Salivation, panting and hyperthermia can also be features. Emesis is rarely safe and as the risks probably outweigh the benefits, the authors would not recommend gastric lavage. Sedation and muscle relaxation are the mainstays of treatment, with anti-epileptic medications proving useful for their sedative effects. Intubation is often performed in severe cases when sedation compromises airway protection. Lipid emulsion therapy should be given due to the lipophilic nature of the toxins. 18

***Metaldehyde***

The recent overturning of plans to ban metaldehyde use in the UK will mean likely continued exposure of pets to this agent.19 Used for baiting slugs and snails it decreases levels of inhibitory neurotransmitter GABA, increases monoamine oxidase activity and decreases noradrenaline and serotonin levels. 9 Absorbed via the gastro-intestinal tract, it induces initial anxiety, followed by tremors, ataxia, muscle fasciculations and seizures. Temporary blindness is also reported.20 With effective decontamination, treatment for prolonged periods is generally not required and the majority of management is focused on controlling tremors and hyperaesthesia. Activated charcoal can limit absorption but the rapid progression of clinical signs often prevents its use due to aspiration risk.

***Bromethalin***

Bromethalin is gaining popularity as a rodenticide in the USA and whilst not commonly used in the UK, it is currently available. 21 Its mechanism of action is different to the anticoagulant rodenticides (e.g. brodifacoum). Once ingested, bromethalin uncouples oxidative phosphorylation, resulting in a complete failure of mitochondrial ATP production. The most important manifestation is in cell membrane sodium/potassium ATPase pump failure. Clinical signs are usually apparent within 2 hours of ingestion, but low doses could result in a delayed presentation. Signs include ataxia, depression, seizure, coma, respiratory paralysis and death. The toxin is very rapidly absorbed, and decontamination is of questionable use beyond 1.5 hours after exposure. Enterohepatic circulation occurs which warrants the use of activated charcoal if clinical signs are not present. There is no antidote, and treatment is largely supportive. Specific treatment for cerebral oedema is warranted, and lipid therapy should be considered. Ginko Biloba was used with success in conjunction with other treatments in one report and has also been shown to provide some protective effect in experimental rat models. 21,22 Although prognosis is extremely guarded, successful treatment in a dog has been reported. 21

**Cardiovascular toxicities**

A number of common toxicants have the capacity to directly cause cardiovascular compromise. Perhaps more frequently, toxicants may cause cardiovascular changes indirectly, in which case the underlying toxicity and cause will require management alongside supportive therapies for the cardiovascular system. Indirect effects could include tachycardia, bradycardia, hypertension, hypotension and arrhythmias. During a major body systems assessment focusing on controlling seizures, securing oxygenation/ventilation and airway protection, cardiovascular priorities common to all intoxications would include intravascular volume resuscitation where necessary, monitoring and correcting electrolyte derangements and continuous ECG and blood pressure monitoring. It is especially important to have excluded hypovolaemia before any form of sedatives or *β*-blocking agents are used.

***Tachycardia***

# Tachycardia may simply result from endogenous catecholamine release, which may stem from the stress of the episode or clinical signs, hospitalisation, or discomfort associated with intoxication. Hyperthermia, which may be apparent in many neurotoxicities, has the capacity to reduce peripheral vascular resistance, cardiac preload and cardiac output, with a resultant tachycardia that will respond to fluid resuscitation and active cooling.23 Tachycardia as a direct result of intoxication is common in amphetamine, cocaine and methylxanthine intoxications. Often the tachycardia is controlled with sedative drugs used to manage excitation, with *β* blocking agents such as esmolol reserved for severe cases. 24 It is important to have excluded hypovolaemia before any form of sedatives or *β*-blocking agents are used however, with careful consideration of potential fluid losses through history taking and physical examination.

***Bradycardia***

There are many reasons that an intoxicated patient may be bradycardic. Gastrointestinal dysfunction may elevate vagal tone, atrial standstill can develop due to hyperkalaemia in patients with acute kidney injury, and patients with raised intracranial pressure can develop hypertension and bradycardia. It is crucial to measure the blood pressure and evaluate an ECG in a patient with bradycardia and clinical signs, before considering any form of intervention. For example, atropine would be contra-indicated in the bradycardic, hypertensive patient with raised intracranial pressure. Bradycardia as a direct result of intoxication would be common in marijuana, digoxin, and β-blocker intoxications.

***Hypertension***

Hypertension is not a particularly common indirect manifestation of a toxicity, except in the event that raised intracranial pressure has developed (e.g. after protracted seizures or cardiorespiratory arrest and development of cerebral oedema). It may be more commonly documented in excitatory and sympatheticomimetic intoxications such as with methylxanthines, amphetamines and cocaine. It will rarely necessitate antihypertensive treatment beyond sedation and *β*-blocking agents where tachycardia is also present. Phenothiazines such as acepromazine would serve as sedatives and antihypertensives concurrently.

***Hypotension***

Hypotension is commonly encountered in the intoxicated patient, most likely because of a loss of vasomotor tone (including iatrogenically during treatment), with or without concurrent loss of intravascular volume (for example in patients with vomiting and diarrhoea). Fluid resuscitation and ongoing fluid therapy would be the mainstays of management in this scenario, but if hypotension persists and loss of vasomotor tone is considered a significant factor, then vasopressor therapy should be instigated. Choice of vasopressor may come down to availability and familiarity, but noradrenaline or dopamine would be reasonable first line choices. Dobutamine would be reserved for cases with cardiac systolic dysfunction and avoided where possible due to pro-arrhythmic properties. It should be noted that all vasopressors have the potential to induce or worsen arrhythmias, and hence every attempt should be made to taper down and stop them as soon as they have served their purpose.

***Arrhythmias***

The most important rule in management of arrhythmias is “*primum non nocere*” – first do no harm. If the arrhythmia is not compromising cardiac output, is improving with time or the patient is not clinically affected, then it is unlikely that anti-arrhythmic therapy is indicated. In the event that worsening ventricular arrhythmias (a common tachyarrhythmia seen in intoxicated patients) are documented, the indications for treatment with lidocaine would be sustained ventricular tachycardia (above 160-170bpm) (Figure 2), progressive, polymorphic ventricular rhythms, and/or R-on-T phenomenon. Accelerated idioventricular rhythm (ventricular beats occurring at a rate above the ventricular escape rate of about 30-50bpm up to 160-170 beats per minute in dogs) does not warrant anti-arrhythmic treatment and the difference between this and true ventricular tachycardia is solely the rate. Ventricular arrhythmias would often be seen in amphetamine and local anaesthetic intoxications.

In the unknown but suspected intoxication with cardiovascular derangements, the first question to answer is whether the cardiac abnormalities are physiological responses or more likely toxicant-induced. Physiology can be managed by supportive measures discussed above, while some toxicity associated effects have specific remedies or management techniques.

Cardiovascular toxicities are slightly more specific and considering the tendency for them to result from human medication ingestion, thankfully their identity and time of ingestion may be known more often than in neurological intoxications. To that effect, sometimes they have a more specific treatment protocol.

**Common toxicities directly affecting the cardiovascular system:**

***Methylxanthines i.e. theobromine and caffeine (chocolate)***

There is a spectrum of clinical signs referable to chocolate ingestion, from initial gastrointestinal signs (vomiting and diarrhoea) within 6 hours of ingestion, through to agitation, tremors and associated hyperthermia, and tachycardia or tachyarrhythmias that could ultimately prove fatal. Treatment is largely supportive, including enhancement of urinary excretion of toxic metabolites with fluid therapy and promotion of urination, as methylxanthines can be re-absorbed across the bladder wall. The vast majority of cases will not require treatment for longer than 12-24 hours. In severe cases with persistent sinus tachycardia, short acting β1 selective blocking drugs such as esmolol may be used. This would be delivered as a continuous rate infusion where ECG and blood pressure monitoring are available, as bradycardia and hypotension would be common adverse effects. Decontamination should be instigated by emesis so long as the patient is not neurologically affected, followed by repeated doses of activated charcoal. It is well worth sourcing a ‘chocolate calculator’ for quick assessment of the risk of toxicity on telephone consultation; dark chocolate containing significant amounts of methylxanthines compared to white and milk chocolate.

***Local anaesthetics***

CNS signs (usually excitatory although seizures, coma and death are possible) are more common side effects of local anaesthetic toxicity when plasma levels rise slowly. However, when toxicity results from intravenous injection, a rapid rise in local anaesthetic levels can cause cardiovascular collapse. Local anaesthetics will prolong the QR interval and QRS complexes, induce bradycardia and atrioventricular blocks and predispose to ventricular arrhythmias. Treatment is supportive (i.e. supporting perfusion and oxygenation, avoiding electrolyte derangements and managing nausea) but intravenous lipid emulsion therapy is specifically indicated in local anaesthetic overdoses, especially when cardiopulmonary resuscitation is being attempted. 25

***Calcium channel blockers and*** *β* ***blockers***

*Calcium channel blockers-* Calcium channel blockers are prescribed frequently in both human and veterinary medicine. There are three broad groups that predominantly have their effects on cardiac myocytes, pacemaker cells and vascular smooth muscle cells. The phenylalkylamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem) tend to cause bradycardia by inhibition of L-type calcium channels in cardiac pacemaker cells and can cause negative inotropy concurrently. Whilst all calcium channel blockers can cause vasodilation of peripheral and coronary vasculature, the dihydropyridines (e.g. amlodipine, nicardipine and nifedipine) have the highest vasodilator potency. For these reasons, a diltiazem or verapamil intoxication is more likely to cause bradyarrhythmias and hypotension, rather than hypotension and associated tachycardia in the case of an amlodipine intoxication. In addition to cardiovascular collapse, calcium channel blockers impair insulin release, creating a hyperglycaemic state and a form of metabolic shock whereby intracellular glucose supplies are depleted.

*β-blockers*- β1-receptors are located primarily in the sinoatrial and atrioventricular nodes, and myocardium. Stimulation induces an increase in heart rate and contractility. β2-receptors are predominantly located in bronchial and vascular walls, where stimulation induces relaxation, and in the pancreas where they promote insulin release. β-blockers such as sotalol and propranolol block both β1 and β2 receptors, while esmolol and atenolol only block β1. β-blocker intoxication therefore reduces myocardial contractility, heart rate and atrioventricular conduction. When β2 blockade is also present, bronchoconstriction and inhibition of insulin release can also occur.

Ultimately both calcium channel blockers and β-blockers have the capacity to cause cardiovascular collapse by massive vasodilation, reduced chronotropy and reduced inotropy. Crucially, the downstream effect of β blockade is inhibition of L-type calcium cells in the heart, hence the mechanisms of toxicity and treatment of both classes is similar.

*Management of calcium channel blocker and β-blocker intoxications*- Emesis would be recommended in asymptomatic patients, with gastric lavage reserved for cases with massive, recent ingestion, +/- an altered level of consciousness that precludes induction of emesis. Note that sustained release formulations of calcium channel blockers may make repeated doses of activated charcoal useful. 26

Alongside intravenous fluids (bolused in the hypotensive patient), intravenous calcium administration is recommended in both calcium channel blocker and β-blocker toxicities, to improve cardiac conduction, inotropy and blood pressure. Typically, 0.5-1ml/kg of 10% calcium gluconate would be administered (slowly to avoid hypotension and arrhythmias) followed by a continuous rate infusion to secure high-normal serum calcium levels. Adrenergic vasopressor drugs targeting increased cardiac contractility (e.g. dobutamine, norepinephrine, dopamine) and increased vasomotor tone (norepinephrine, dopamine) may be indicated. Insulin therapy is recommended as it will promote intracellular glucose uptake, allowing an increase in inotropy and peripheral vascular resistance. The recommended dose would be 1IU/kg neutral insulin initially, followed by 1IU/kg/hr for 1 hour, and 0.5U/kg/hr until no longer required. 27 Glucagon has also been recommended as it has inotropic, chronotropic and dromotropic effects on the heart. Intralipid is of theoretical benefit when traditional management is not effective. Calcium channel blockers and β-blockers are variably lipid soluble, however, with propranolol and verapamil being the most soluble.

***Serotonergic medications***

Serotonergic medications have mood altering effects by multiple convergent mechanisms; increasing serotonin production (e.g. L-tryptophan, 5HTP), inducing serotonin release (e.g. amphetamines, cocaine, ecstasy), inhibiting serotonin metabolism (monoamine oxidase inhibitors e.g. tranylcypromine), inhibiting serotonin re-uptake (serotonin re-uptake inhibitors e.g. fluoxetine, tricyclic antidepressants (TCAs) e.g. amitriptyline, trazadone), or stimulating serotonin receptors directly (e.g. LSD). They tend to be rapidly absorbed with narrow safety margins, so decontamination and activated charcoal are indicated in documented overdoses. Clinical signs are predominantly neurological, gastrointestinal and cardiovascular.28 Hyperthermia and disseminated intravascular coagulation (platelet activation is triggered by serotonin, in addition to hyperthermia) are possible. Treatment of the neurological symptoms typically involves sedation and antagonism of serotonin using cyproheptadine (1.1mg/kg PO or rectally (dog)). Autonomic instability can manifest as tachycardia and hypertension; if sedation and serotonin antagonism does not control this, β-blockers may be indicated. More profound cardiovascular collapse including bradycardia with hypotension can be seen in TCA toxicity. Intralipid should be considered in cases refractory to traditional management.

***Muscle relaxants (e.g. Baclofen)***

# Baclofen is a commonly prescribed muscle relaxant in people. It stimulates the GABAA receptor, hyperpolarising neuronal cell membranes and increasing inhibitory tone. Cardiovascular manifestations of toxicity (alongside vomiting, sedation, respiratory arrest coma and seizures) include hypotension, hypertension, bradycardia, tachycardia and conduction abnormalities. Bradycardia tends to be very responsive to atropine. Hypotension is managed with intravenous fluid therapy and vasopressor therapy. Hypertension of above 160-180mmHg particularly with evidence of target organ damage would necessitate vasodilator treatment with sodium nitroprusside or amlodipine, for example. Amlodipine may be administered at the same dose per rectum, dissolved in water, where necessary. 29 Intralipid has been reported to be of benefit and one dose of activated charcoal is likely sufficient due to a lack of enterohepatic circulation. 30

**Conclusion**

Specific toxic doses are not included in this article and contact with the VPIS (https://www.vpisglobal.com) is advised to allow discussion on a case-by-case basis. Diagnostic/confirmatory testing on body fluids such as blood, vomitus and urine are increasingly available with twenty-four-hour turnaround times and extensive toxicology panels offered by the Veterinary Pathology Group (SynLab). A careful approach to the deranged physiology with stabilisation of major body systems can make these cases very rewarding to manage.

**Tables and Figure legends**

**Table 1:** Cardiovascular and neurological toxicants and their common clinical signs. CNS; central nervous system, MDMA; 3,4-Methylenedioxymethamphetamine,

 SRI; serotonin reuptake inhibitor, SNRI; serotonin nor-epinephrine reuptake inhibitor, TCA; tricyclic antidepressant, MAO; monoamine oxidase inhibitor.

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| **Toxin** | **Common Effects** |
| **Ethanol** | Depression, ataxia, lethargy, sedation, hypothermia. |
| **Ethylene glycol (antifreeze)** | CNS depression, incoordination and ataxia. If severe, somnolence and coma. Seizures possible. |
| **Anticholinergics (Plants e.g. deadly nightshade, angel’s trumpet. Drugs e.g. atropine, tropicamide)** | Disorientation, agitation, ataxia, coma, respiratory failure, seizures. |
| **Bromethalin (rodenticide)** | Low-moderate doses can cause decreased proprioception. More severely affected will be comatose. Hyperexcitability, hyperaesthesia, tremors, seizures. Decerebrate when terminal. |
| **Carbon monoxide** | Lethargy, depression, syncope, unconsciousness, seizures. |
| **Cyanide** | Loss of consciousness with fixed dilated pupils. Seizures possible. |
| **Hops** | Anxiety, seizures, malignant hyperthermia. |
| **Amitraz** | CNS depression at lower doses. CNS excitation at higher doses. |
| **Pyrethrin and Pyrethroids** | Hyperaesthesia, muscle twitches/tremors, seizures. |
| **Lead** | Behavioural changes, polyneuropathy, blindness, coma, seizures, agitation, vestibular signs, aggression, tremors. |
| **Macadamia nuts** | Hindlimb weakness and ataxia, muscle tremors, stiffness. |
| **Avermectins (Ivermectin, selamectin, doramectin, abamectin)** | Higher doses cause inhibitory effects: CNS depression, coma, weakness and flaccid paralysis. Early signs are excitatory: hyperaesthesia, hyperactivity, tremors. |
| **Metaldehyde (slug bait)** | Coma possible if late. Hyperaesthesia, muscle fasciculations, tremors, seizures, mydriasis  |
| **Tremorgenic mycotoxins (mouldy food)** | Muscle tremors, seizures. Sinus tachycardia. |
| **NSAIDs (ibuprofen, naproxen, salicylate)** | At high doses: depression, coma, seizures. (AKI) |
| **Cocaine** | Restlessness, hyperactivity, tremors, seizures. Tachycardia, hypertension. |
| **Marijuana** | Depression, disorientation, lethargy, ataxia and coma if severe. Hyperaesthesia, nystagmus, photophobia and seizures also possible. (Urinary incontinence). |
| **MDMA/amphetamines** | Restlessness, pacing, panting, pronounced hyperactivity, vocalization, tachypnoea, tremors, hyperthermia, seizures, and potentially death. Some animals can show signs of depression. Tachycardia, VPCs, hypertension, hypotension. |
| **Salt toxicity (e.g. table salt, paintball ingestion)** | More commonly hyperexcitable signs such as ataxia, tremors and seizures. |
| **Serotonergic medications. SRIs: Fluoxetine, sertraline. SNRIs: duloxetine. TCAs: amitriptyline, clomipramine, trazodone. MAOs: tranylcypromine)** | Sedation and coma possible. Agitation, tremors, hyperexcitability, hyperaesthesia common. Vomiting, diarrhoea, hyperthermia. Muscular rigidity at higher doses, seizures possible. Autonomic instability – tachycardia, bradycardia, hypertension, hypotension. |
| **Chocolate (methylxanthines i.e. theobromine and caffeine)** | Gastrointestinal, excitation, hyperthermia, tremors, seizures, tachycardia, tachyarrhythmias. Coma if severe and late. |
| **Local anaesthetics** | Excitation, seizures, coma, bradyarrhythmia, ventricular arrhythmias. |
| **Calcium channel blockers** | Bradyarrhythmia, hypotension, tachycardia, hyperglycaemia. |
| *𝛃-***blockers** | Bradyarrhythmia, bronchoconstriction, hyperglycaemia. |
| **Baclofen (muscle relaxant)** | Sedation, vocalisation, seizures, coma. Hypertension, hypotension, tachycardia, bradycardia, conduction abnormalities. |
| **Cardiac glycosides (e.g. foxgloves, digoxin)** | Restlessness and disorientation possible, uncommonly seizures. Bradycardia, hypotension, gastrointestinal. |

**Table 2:** Specific treatments for neurological and cardiovascular toxicants. ICP; intra cranial pressure

|  |  |  |
| --- | --- | --- |
| **Therapy** | **Dose**  | **Toxicant indications** |
| Seizures |  |  |
| Diazepam  | 0.25-0.5mg/kg IV bolus0.2-0.5mg/kg/hr CRI |  |
| Midazolam | 0.25- 0.5mg/kg IV bolus0.2-0.5mg/kg/hr CRI0.2mg/kg Intranasally |  |
| Propofol | 1-6mg/kg IV bolus (to effect)0.05-0.4mg/kg/hr | For seizures not controlled by benzodiazepines |
| Phenobarbitone  | 2-4mg/kg IV as necessary up to 16mg/kg per day for first 24 hoursReduce to 2.5mg IV/PO BID  |  |
| Levetiracetam | 20mg/kg IV/PO TID |  |
| Tremors |  |  |
| Methocarbamol | 30-50mg/kg IV prn/to effect to control tremors. Maximum 24hr dose of 330mg/kg  | Centrally acting muscle relaxant If IV is not available, oral tablets given rectally (dissolved in water) has been used with success (same dose as IV) |
| Increased ICP  |  |  |
| Mannitol  | 0.5-1g/kg IV over 15 minutes  |  |
| Hypertonic saline | 1-3ml/kg IV of 7% over 10-15 mins |  |
| Bicarbonate therapy  | SBE x 0.3 x BW (kg), administer 1/3 to 1/2 of dose over 30mins | For severe metabolic acidosis (<7.0-7.1, where close monitoring of acid base status is available), care with hypoventilation and hypernatraemia  |
| Antidotes |  |  |
| Atipamezole | Dogs: 50mg/kg IM | Amitraz |
| Atropine  | 0.1-0.5mg/kg (give ¼ dose IV and rest IM or SC) | Acetylcholinesterase inhibition |
| Pralidoxime (2-PAM) | Dog/cat- 20mg/kg IM or slow IV initial dose then q8-12h subsequent IM or SC | Nicotinic signs in OP toxicity |
| Ethanol  | Dogs: 20% ethanol 5.5ml/kg IV q4h for 5 treatments then q6hr for 4 treatments (or same total dose as CRI)* Low dose protocol 30% ethanol 1.31ml/kg slow bolus then 0.42ml/kg/hr for 48h
* Alternate protocol: 300mg/kg bolus then 100mg/kg/hr

Cats: 20% ethanol 5ml/kg IV q6h for 5 treatments then q8h for 4 treatments | Ethylene glycol toxicity |
| Fomepizole (4-Methylpyrazole)  | Dogs: Load with 20mg/kg IV* at 12 h 15mg/kg IV
* at 24h 15mg/kg IV
* at 36 h 6mg/kg IV

Cats: Load with 125mg/kg IV* at 12, 24 and 36h give 31.25mg/kg
 | Ethylene glycol toxicity |
| Chlorpromazine  | 0.5mg/kg IV, IM, SC q6h | Serotonin syndrome |
| Cyproheptadine | Dogs: 1.1mg/kg PO or rectal q 6-8h if effectiveCats: 2-4mg/kg q4-6h | Serotonin syndrome |
| Yohimbine | Dog: 0.1mg/kg IV repeat prn | Amitraz |

**Figure Legends**

Figure 1. Imaging findings that are consistent with aspiration pneumonia. Thoracic ultrasound identifying a shred sign (top left) and bronchogram (bottom left). Radiographic evidence of aspiration pneumonia in an intoxicated patient (right).

Figure 2. Onset of ventricular tachycardia (>300bpm) in a dog. Paper speed: 50mm/s.

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