CPD article

# Poisons affecting the neurological system

The brain is susceptible to a variety of poisons. Sedating drugs and chemicals can cause central nervous system (CNS) depression while other substances can cause CNS stimulation, including seizures. These are of particular concern since intractable seizure activity may cause complications, with pyrexia resulting in secondary damage to other organs. The common poisons discussed here that cause neurological effects are metaldehyde and tremorgenic mycotoxins, which can cause rapid onset seizures; cannabis, which can cause prolonged sedation in companion animals; permethrin, which is associated with prolonged seizures, particularly in cats; and ivermectin, which can cause CNS depression, blindness and seizures. Treatment is supportive in most cases; care should be taken when considering the use of emetics since there is a risk of aspiration in seizuring animals. Control of seizure activity is a priority, while intravenous lipid emulsion may also be useful.

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Many different substances can cause a variety of neurological effects following overdose or accidental exposure. These effects can range from central nervous system (CNS) depression to CNS stimulation and seizures. Complications of prolonged seizure activity include severe pyrexia, which can result in rapid cellular necrosis; rhabdomyolysis, which can lead to acute kidney injury; and disseminated intravascular coagulation (DIC). These complications can lead to multi-organ failure.

Neurological effects from poisons can occur through direct effects on receptors, or as a result of metabolic disturbances. There are species and breed-specific factors that may influence susceptibility to some poisons. Some of the common poisons associated with neurological effects are discussed below; other substances that can cause neurological effects in companion animals are listed in *Box 1*.

Lipid emulsion may be useful in the management of poisoning with some substances affecting the neurological system, since many are lipophilic. A measure of lipophilicity is the log P; the higher the log P the more lipophilic a compound. If the log P is >1 then lipid emulsion may be useful, although it is not used for substances with a long biological half-life, even if lipophilic.

## Unknown mechanism of neurological effects

### Metaldehyde

Metaldehyde is a common ingredient of molluscicide preparations and is typically formulated as blue/green pellets (*Figure 1*) containing 1.5–8% w/w metaldehyde in a bran/wheat filler. In the USA, some products also contain other compounds (e.g. carbaryl, a carbamate), so it is important to obtain specific product details. The use of metaldehyde is currently under discussion in the UK, as the Expert Committee on Pesticides and the Health and Safety Executive advised that metaldehyde poses an unacceptable risk to birds and mammals. A ban on outdoor use of metaldehyde slug pellets to come into force in spring 2020 has recently been overturned, but this may change.

#### Mechanisms of toxicity

The mechanism of metaldehyde toxicosis in mammals is not clearly understood. In mice, metaldehyde exposure has been linked to a decrease in the concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), noradrenaline and serotonin (5-hydroxytryptamine, 5-HT), as well as increased monoamine oxidase activity (Homeida and Cooke, 1982a; 1982b). Disruption of the GABAergic system may cause the convulsant activity seen in metaldehyde exposures (Homeida and Cooke, 1982b; Sparks et al, 1996). It may be metaldehyde itself or an unknown metabolite that is responsible for the effects observed in metaldehyde poisoning. Hyperthermia resulting from the increased muscular activity may also be a significant factor in metaldehyde poisoning. Severe metabolic acidosis also occurs; this may be the underlying cause of the hyperpnoea and CNS depression seen in severe poisoning.

#### Clinical effects

Onset of signs of metaldehyde toxicosis may be very rapid, often within 30 minutes of ingestion, but may be delayed for up to

## Box 1. Other potential toxicological causes of neurological effects in companion animals

- Any substance causing CNS depression e.g. ethanol, sedative drugs such as benzodiazepines, opioids, antidepressants
- Recreational drugs
- Baclofen and other muscle relaxants
- Alphachloralose
- Cycads
- Mefenamic acid
- 5-Fluorouracil
- Mebeverine
- Amphetamines and similar, e.g. methylphenidate and lisdexamfetamine
- 5-Hydroxytryptophan (5-HTP)
- Sympathomimetics (phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine)
- Fungi containing psilocybin or ibotenic acid
- Sodium chloride (as a result of hypernatraemia)
- Xylitol (as a result of hypoglycaemia)
- Methylxanthines (caffeine, chocolate)
- Moxidectin, doramectin and milbemycin, particularly in susceptible dog breeds (collies and related breeds)
- Isoniazid (seizures in dogs)
- Potentially any substance causing hypoxia

*Figure 1. Metaldehyde slug bait can cause rapid-onset seizures.*

3 hours. Recovery may take several days (Bates et al, 2012). In fatal cases death can occur in a few hours, but may occur up to 36 hours (Bates et al, 2012).

Common signs are hypersalivation, vomiting, diarrhoea (often discoloured greeny-blue), ataxia, panting, tremor, twitching, muscle spasms or fasciculation, convulsions or opisothotonus with hyperthermia. Respiratory effects (tachypnoea, dyspnoea, hyperventilation and respiratory depression) are less commonly reported; cardiac effects (including tachycardia or bradycardia) also can occur (Bates et al, 2012).

Convulsions can last up to 72 hours but on average last 15 hours (Bates et al, 2012). Animals with prolonged seizure activity are at risk of complications that could result in multi-organ failure.

Metabolic acidosis is a common finding in metaldehyde toxicosis. Elevated liver enzymes can occur (probably due to stress or barbiturate therapy). Elevated creatine kinase (CK) and lactate dehydrogenase (LDH) levels can occur as a result of increased muscle activity. Renal impairment is rare, and usually secondary to hyperthermia. Temporary blindness is occasionally reported (Bishop, 1975; Bates et al, 2012) and is probably caused by seizure activity rather than a toxic effect of metaldehyde itself. Apparent memory loss has also been reported (Bishop, 1975).

Cause of death in metaldehyde poisoning is often said to be respiratory failure (Booze and Oehme, 1985; Dolder, 2003), but this is generally not the case; rather it may be a result of complications of prolonged seizure activity such as hyperthermia or DIC. Other problems reported in fatal cases include multi-organ failure, complications of aspiration, pulmonary oedema and thromboembolism (Bates et al, 2012). The fatality rate in dogs with metaldehyde toxicosis is approximately 14–17% (James, 1955; Studdert, 1985; Robertson et al, 1992; Yas-Natan et al, 2007; Bates et al, 2012).

### Treatment

If the dog is presented to the surgery within 1 hour of exposure and is asymptomatic, then induction of emesis may be considered, with caution. Administration of an emetic after this time should be avoided, because of risk of convulsions. Gastric lavage should be considered, particularly if the dog is thought to have ingested anything other than a very small quantity or has developed moderate to severe signs rapidly. Activated charcoal is best avoided in conscious animals, because of the risk of rapid-onset convulsions. If gastric lavage is performed, then activated charcoal can be left in the stomach after lavage.

The mainstays of treatment of metaldehyde toxicosis are control of convulsions and prevention of complications of prolonged seizure activity. Several different drugs are used in the control of convulsions. In a review of cases in dogs, almost half the animals requiring anticonvulsant therapy required more than one sedative or anaesthetic (Bates et al, 2012). Ideally, animals should be kept under anaesthetic for about 6–12 hours, then the dose may be slowly tapered off and the animal observed closely to see if convulsions recur. If they do then the dosing should be resumed as before.

Diazepam is an appropriate first-choice drug to use in any animal with twitching or seizure, and may be considered for cases presenting with mild signs only (*Table 1*). Propofol should be used immediately for any case presenting with moderate or severe signs, and administration may allow gastric lavage. Animals may need to be maintained on propofol for some time, so it is often easier to use a constant-rate infusion. Midazolam can be added to the therapy in animals that continue to have seizures even when receiving propofol. Isoflurane can be considered as an alternative option to propofol or propofol/midazolam. In severe cases, use of barbiturates may also be considered as an alternative therapy. In the past, before agents such as propofol were available, this was one of the major methods of controlling convulsions in metaldehyde intoxications in dogs. Methocarbamol, a centrally acting muscle relaxant, can be used with diazepam or propofol.

Where possible, blood gases and body temperature should be monitored. Standard cooling measures should be instituted for

any animal with pyrexia; however, the temperature should fall once convulsions are controlled. To help prevent development of pulmonary oedema it is advisable to turn the animal every few hours, rotating between lateral and sternal recumbency. Acidosis is managed by restoring tissue perfusion through administration of intravenous (IV) fluids containing a bicarbonate precursor (such as lactate) or, if required, sodium bicarbonate therapy. Once other signs are controlled as above, acidosis may resolve without the need for bicarbonate therapy. Oxygen therapy may be required in animals with respiratory distress.

Where possible, baseline liver enzyme concentrations should be measured as soon after admission as practical and repeated at 24–48 hours, and beyond as required. Usually, abnormalities resolve with supportive care only. If there is significant, prolonged pyrexia then renal function should be checked, because of the risk of complications.

Metaldehyde is not lipophilic (the log P is very low, only 0.12), therefore it is unlikely that lipid infusion would be useful. There are anecdotal reports of it having both a positive effect and no effect in dogs with metaldehyde toxicosis (VPIS data). Haemodialysis has been shown to remove metaldehyde from canine plasma in vitro (Mauser et al, 2016) and a recent review of 11 cases found that haemodialysis significantly decreased the requirement for anaesthesia and length of hospitalisation in dogs with metaldehyde intoxication (Teichmann-Knorrn et al, 2020). However, it will not be available in most veterinary cases.

## Tremorgenic mycotoxins

Mycotoxins are fungal metabolites that cause toxic effects in humans and animals. Tremorgenic mycotoxins of clinical significance are penitrem A and roquefortine. These may be present in a variety of sources, and tremorgenic mycotoxicosis has been confirmed or suspected in dogs following ingestion of the following: food waste and rubbish (Lowes et al, 1992; Walter, 2002); mouldy food (Hocking et al, 1988; Naude et al, 2002) (*Figure 2a*), particularly mouldy dairy products (Arp and Richard, 1979; Puls and Ladyman, 1988; Young et al, 2003) (*Figure 2b*), mouldy fallen fruit and nuts (Richard et al, 1981; Munday et al, 2008; Eriksen et al, 2010) and compost (Boysen et al, 2002) (*Figure 2c*). Death has been reported in several cases (Puls and Ladyman, 1988; Lowes et al, 1992).

*Figure 2. Common sources of tremorgenic mycotoxins: a) mouldy bread; b) mouldy dairy products (e.g. cream cheese; and c) compost.*

### Mechanisms of toxicity

The mechanism of action of tremorgenic mycotoxins is unclear and may vary with the mycotoxin. Penitrem A may interfere with the release of neurotransmitters (glutamate, aspartic acid and GABA) (Norris et al, 1980; Bradford et al, 1990) and it has also been shown to induce tremors in mice by acting as an antagonist to production of the neurotransmitter glycine (Catovic et al, 1975). The tremorgenic mycotoxins may also act synergistically.

**Table 1. Dosages of anticonvulsant drugs**

| Drug | Dogs | Cats |
|---|---|---|
| Diazepam | 0.5–1.0 mg/kg IV or rectally. Repeat every 10 minutes if no clinical effect, up to 3 times<br>CRI 0.5–2 mg/kg/h, titrated to effect | 0.5–1.0 mg/kg IV or rectally. Repeat every 10 minutes if no clinical effect, up to 3 times<br>CRI 0.5 mg/kg/h, titrated to effect |
| Midazolam | 0.2–0.3 mg/kg IV or rectally. Repeat every 10 minutes if no clinical effect, up to 3 times<br>CRI 0.3 mg/kg/h | 0.2–0.3 mg/kg IV or rectally. Repeat every 10 minutes if no clinical effect, up to 3 times |
| Propofol | 6-7 mg/kg IV<br>CRI 0.1–0.4 mg/kg/min | 8 mg/kg IV<br>CRI 0.1–0.4 mg/kg/min |
| Phenobarbital | 18–24 mg/kg, then 2–3 mg/kg every 12 hours. Give loading dose as 12 mg/kg slow IV, then 20 min later two further doses of 4–6 mg/kg by slow IV injection, 20 minutes apart | |
| Methocarbamol | 55–220 mg/kg orally, repeated as required to a maximum dosage of 330 mg/kg/day. Tablets can be crushed, mixed with saline and given rectally, if required<br>Same dose IV, at a rate of ≤ 2 mL/min to effect | |

CRI: constant rate infusion; IV: intravenously

### Clinical effects

The onset of clinical effects after ingestion of tremorgenic mycotoxins can be rapid, usually within 30 minutes, but sometimes takes up to 3 hours (Puschner, 2004; Eriksen et al, 2010).

Common signs of tremorgenic mycotoxicosis include vomiting, irritability, ataxia, whole-body muscle tremors, rigidity with hyperextension of extremities, hyperactivity, hyperaesthesia, tachycardia, panting, tachypnoea, nystagmus and blepharospasm. Dilated pupils have been reported in some cases and severe tremors, opisthotonus, convulsions and coma with paddling may occur in severe poisoning. Aspiration is a potential complication while increased muscle activity can lead to hyperpyrexia, exhaustion, rhabdomyolysis, dehydration, hypoglycaemia, and raised levels of LDH, CK and liver enzymes. Most animals with tremorgenic mycotoxicosis recover within 24–48 hours with aggressive treatment (Puschner, 2002), particularly if treatment is started soon after ingestion. In some cases recovery may take 3–4 days (Walter, 2002; Eriksen et al, 2010), but occasionally it can be months. In two cases, for example, ataxia and tremor reportedly took about 6 months to resolve in one dog, while ataxia was still present more than 3 years after the poisoning incident in another (Eriksen et al, 2010).

### Treatment

Emesis can be considered after ingestion of mouldy food or compost, but only if ingestion was recent and the animal is asymptomatic. A gastric lavage should be considered if the quantity ingested is large or the animal is symptomatic. Repeat dose activated charcoal should also be considered, depending on the condition of the dog, as the mycotoxins undergo enterohepatic recirculation (Laws and Mantle, 1987; Laws et al, 1987) and this can be interrupted by repeated administration of charcoal. Antiemetics may be required in vomiting animals, to reduce the risk of aspiration pneumonia.

Supportive treatment should include the usual care of a comatose patient, adequate hydration and monitoring of respiration and temperature (cooling measures for hyperpyrexia in combination with high dose sedation may precipitate hypothermia). Ventilatory support will be required in animals with severe respiratory depression.

Diazepam is ineffective in most cases of tremorgenic mycotoxicosis, so other drugs such as propofol, barbiturates (e.g. phenobarbital) and methocarbamol can be used (*Table 1*). Tremorgenic mycotoxins are lipophilic so lipid emulsion is recommended. In a study of 53 dogs with suspected tremorgenic mycotoxicosis there was clinical improvement recorded after administration of lipid emulsion in 96% of cases within a median time of 4 hours (Kormpou et al, 2018).

## Cannabis

Cannabis is the collective term for all psychoactive substances derived from the dried leaves and flowers of the plant *Cannabis sativa* or hemp (Fitzgerald, 2007) (*Figure 3*). Marihuana (marijuana) refers to any part of the plant used to induce effects; hashish is the dried resin from the flower tops. Tetrahydrocannabinol (THC) is the toxic component. Cannabidiol (CBD) oil is also produced from *Cannabis sativa* but from strains that contain low concentrations of THC. The active component of CDB oil is cannabidiol, a non-psychoactive cannabinoid.

*Figure 3. Cannabis, in various forms, is commonly used recreationally and medicinally. It can cause prolonged sedation in pets.*

Marijuana is a commonly-used recreational drug among humans, and animals may be exposed following ingestion or accidental inhalation of smoke. Dogs less than 1 year of age are the most likely companion animal to ingest marijuana (Kisseberth and Trammel, 1990; Janczyk et al, 2004). Baked goods containing cannabis (e.g. cannabis cookies, space cake) may also be attractive to animals (Jones, 1978; Godbold et al, 1979; Ashton, 2001; Weston, 2003; Janczyk et al, 2004; Kruidenier et al, 2008; Taylor, 2011). Intentional intoxication of small animals using secondhand smoke has also been reported (Schwartz and Riddle, 1985; Buchta, 1988). In America there has been an increase in the number of cases of marijuana toxicosis in dogs following legalisation for human use in some states (Meola et al, 2012).

### Mechanism of toxicity

The exact mechanism of action of the THC is not clear. The actions may be linked to changing concentrations of biogenic amines in the CNS (Kisseberth and Trammel, 1990). In the CNS, THC affects a variety of neurotransmitters, including dopamine, serotonin and GABA. The activity of GABA, an inhibitory neurotransmitter, is increased by THC, resulting in CNS depression. Additionally, THC binds specific receptors in the cerebellum and frontal cortex (Dumonceaux and Beasley, 1990; Kisseberth and Trammel, 1990).

### Clinical signs

Signs of cannabis intoxication can occur 30–90 minutes after ingestion (Donaldson, 2002) and within 6–12 minutes if inhaled (Janczyk et al, 2004). Dogs who ingest a small dose of plant material may recover within 24 hours, but those ingesting large doses may show clinical signs for several days (Kisseberth and Trammel, 1990; Burrows and Tyrl, 2001; Volmer, 2009). Recovery occurs within 72–96 hours (Donaldson, 2002; Janczyk et al, 2004; Sturgeon and Campbell, 2008). Most animals exposed to second-hand smoke recover within a few hours.

Depression of the CNS, ataxia (often pronounced in the hind limbs), and bradycardia are the most common signs in animals exposed to cannabis. This depression may alternate with CNS stimulation and/or hyperaesthesia (Donaldson, 2002). Behavioural changes in dogs include aggression, agitation, barking and hallucinations. In a study of 125 dogs with cannabis ingestion, almost half had urinary incontinence (Meola et al, 2012). Other signs

include weakness, drowsiness, dilated pupils, conjunctival injection, photophobia, tachycardia, vomiting, hypersalivation, faecal incontinence, tremor, twitching and hypothermia. Hypothermia is dose-related, therefore maybe be a useful clinical indicator of the severity of the toxicosis (Thompson et al, 1973; Godbold et al, 1979). There may also be hyperthermia, and rarely convulsions. Later there may be deep depression and bradycardia. Increased appetite may be noted in animals recovering from cannabis intoxication.

Although recovery can be prolonged, most dogs with cannabis toxicity recover (Fitzgerald et al, 2013). Deaths have been reported in dogs after ingestion of baked chocolate cookies or brownies made with marijuana butter (Meola et al, 2012). Other ingredients of cannabis-containing baked goods, such as xylitol or chocolate, may also present a risk to dogs (Bates, 2015; 2019).

### Treatment

Emesis may be induced within 1 hour of ingestion provided the animal is asymptomatic (McKnight, 2003). Any emesis once the animal is symptomatic is not advised, because of the increased risk of aspiration of vomitus in animals with significant CNS depression (Llera and Volmer, 2006). It should be noted that emetics may not always be effective, as THC can have an anti-emetic action. Use of absorbents is also recommended, depending on the clinical condition of the animal. Repeated doses may be effective, as THC undergoes enterohepatic recirculation (Garrett and Hunt, 1977; Fabritius et al, 2012).

Treatment thereafter is largely supportive. Sedation using diazepam (*Table 1*) may be given where necessary e.g. to control agitation, hyperaesthesia, tremors and seizures (Janczyk et al, 2004) and where possible the animal should be kept in a relatively quiet, dark environment (Poppenga, 2001). Cardiac function, rectal temperature and respiratory function should be monitored (Llera and Volmer, 2006). Intravenous fluid may be required in animals that become hypotensive or dehydrated after frequent vomiting and bouts of diarrhoea (Donaldson, 2002).

Lipid infusion has been used successfully in canine cases of severe cannabis toxicity (Meola et al, 2012).

## Effects on specific receptors or membrane proteins

### Permethrin

Permethrin is a pyrethroid (a synthetic pyrethrin derived from chrysanthemum flowers) and is used as an insecticide in dusting powders, liquids, bait stations, and sprays, and to be used directly on animals as spot-on treatments, shampoos, flea sprays or flea collars. Although permethrin poisoning commonly occurs in cats, poisoning with this and related compounds occasionally occurs in dogs (Klainbart et al, 2014).

Cats are typically poisoned with permethrin when they come into contact with a canine spot-on flea treatment. This usually occurs after the product is applied to the cat in error (*Figure 4*) or after the cat comes into contact with a treated dog. There are a few products containing permethrin that are licensed for use in cats (mostly flea collars and flea powders). Products containing a low percentage (1% or less of permethrin) do not seem to cause the signs seen with canine spot-on products, which in contrast contain much higher concentrations (e.g. some spot-on products contain 744 mg/mL, so are 74.4% permethrin). Toxicity has also been reported with spot-on products that contain 45–65% permethrin (Meyer, 1999). Individual response in cats is variable and toxicity can occur from one drop of a high-concentration canine spot-on product (Anadón et al, 2009).

#### Mechanisms of toxicity

The toxic effects of permethrin are caused by alteration of the kinetics of voltage-dependent sodium channels in nerve membranes, which causes repetitive discharges or membrane depolarisation. Some pyrethroids may also inhibit GABA receptors. This inhibits the GABAa-receptor-mediated chloride ion influx, the physiological function of which is to induce presynaptic inhibition. Loss of this inhibition can lead to hyperexcitability of nervous tissue; this may be the mechanism by which these compounds produce convulsions.

In mammals, permethrin is rapidly biotransformed and detoxified by ester hydrolysis or oxidation. As a result, it is of relatively low toxicity in most mammals. Cats are more susceptible to toxic effects than dogs and effects are more common in young cats (<4 years, particularly <1 year) but the reason for this is unclear. Dermal exposure is the most common route in cats but although there is probably some dermal absorption some permethrin may be ingested via grooming. The feline liver is relatively inefficient at glucuronide conjugation leading to slow excretion and accumulation of permethrin metabolites and may be the reason for the common occurrence of toxicity in cats.

#### Clinical effects

Signs of permethrin toxicosis usually start within 1–3 hours but are sometimes delayed up to 36 hours. The duration of effects is generally 1–3 days, but can be longer, although these data were derived from cases before the use of lipid emulsion.

Common signs of permethrin poisoning include vomiting, diarrhoea, hypersalivation, thirst, ataxia, incoordination, dilated pupils, tachycardia, hyperexcitability, hyperaesthesia, hyperthermia, tachypnoea, tremor, twitching, muscle weakness and fasciculations, convulsions and respiratory distress (as a result of weakness of respiratory muscles). Rarer effects include hallucinations, temporary blindness, hypothermia (possibly caused by poor drying

*Figure 4. Permethrin toxicosis may occur after accidental use of a canine spot-on product on a cat.*

after washing), cardiac arrhythmias and cardiac arrest. Prolonged seizure activity could result in cerebral oedema, irreversible brain damage and myoglobinuria-induced nephropathy (Richardson, 1999).

Dermal exposure to permethrin products may also cause local irritation and alopecia, possibly caused by the solvent vehicle.

### Treatment

After ingestion, permethrin is rapidly absorbed and so emetics and activated charcoal are unlikely to be of use.

Cats with tremors or seizures should be stabilised before decontamination.

Dermal exposure is common in cats and in these cases they should be washed with copious amounts of lukewarm water and detergent (permethrin is not water-soluble). The use of hot water should be avoided as this increases dermal perfusion and may result in increased dermal absorption. Cats with long hair may need to have exposed areas clipped. Care should be taken to dry the animal well. A decrease in body temperature may exacerbate effects, because there is an inverse relationship between sodium influx and temperature (Whittem, 1995). Following decontamination the cat should be collared to prevent grooming and should be isolated from other animals to prevent cross-contamination.

Thereafter, treatment is essentially symptomatic and supportive, with the aim of controlling CNS effects. Care should be taken to maintain hydration and body temperature. Pyrexia as a result of increased muscular activity may cause cerebral oedema leading to continued convulsions. Cooling measures should be used carefully, as a low body temperature may lead to increased toxicity.

Diazepam may be of use to control increased muscular activity (twitching, fasciculation or convulsions), but it is often ineffective in severe cases. Methocarbamol is commonly used (Volmer et al, 1998; Richardson, 1999; Hansen, 2013). If injectable methocarbamol is unavailable, oral tablets can be crushed, mixed with saline and given rectally (*Table 1*).

Lipid infusion is recommended in severe permethrin toxicosis; it has been used successfully in a number of cases of permethrin poisoning in cats (Brückner and Schwedes, 2012; Haworth and Smart, 2012; Kuo and Odunayo, 2013; Muentener et al, 2013; DeGroot, 2014). A randomised, controlled clinical trial in cats with permethrin toxicity compared cats treated with and without lipid infusion. The study used a specially designed and validated system describing six clinical stages of poisoning. The study found that cats treated with lipid infusion improved earlier than cats that did not receive lipid (Peacock et al, 2015). Early use of lipid infusion is recommended if the exposure is thought to be significant, the cat has significant neurological signs, or it is failing to respond to other therapies. Rapid improvement can occur in cats with permethrin poisoning given intravenous lipids (Haworth and Smart, 2012; Muentener et al, 2013).

## Ivermectin

Ivermectin is an avermectin antiparasitic agent and dogs (and less commonly cats) may be exposed via ingestion of ivermectin directly (often spilled or dropped by treated horses, for example); from ingestion of the faeces of treated animals; or by parenteral exposure.

### KEY POINTS

- Many substances can cause a wide variety of neurological effects ranging from CNS depression or stimulation and seizures.
- Management will depend on the severity of clinical signs, but control of seizure activity is essential to prevent complications.
- The decision to induce emesis should be assessed carefully because of the risk of aspiration in animals with, or at risk of, seizures.
- Intravenous lipid emulsion can be used for many substances that cause neurological effects following overdose or accidental exposure.

### Mechanism of toxicity

Avermectins are thought to act in mammals by potentiating the release and binding of GABA-gated chloride channels in the CNS (Snowden et al, 2006), causing diffuse cerebellar and cerebral cortex dysfunction. In mammals avermectins do not readily cross the blood–brain barrier, but some breeds (such as collies and related breeds) are particularly susceptible to ivermectin toxicosis. This is because they have a deletion of the ABCB1 (ATP-binding cassette superfamily, formerly the multi-drug-resistance gene, MDR1) (Mealey et al, 2001; Mealey, 2008). This codes for P-glycoprotein, which is present in the membrane of the blood–brain barrier and limits penetration of substances into the brain. Changes in expression of P-glycoprotein allow increased uptake of ivermectin into the brain (Edwards, 2003). Susceptibility is only found in dogs that are homozygous for the mutation (Mealey et al, 2001).

The cause of blindness in ivermectin toxicity is not known, but both intracranial and retinal processes appear to be involved (Kenny et al, 2008).

### Clinical effects

All breeds develop the same clinical signs, but susceptible breeds show signs at lower doses than non-susceptible breeds.

Onset of ivermectin toxicosis may occur within 12 hours of oral exposure with signs progressing over the following 12–24 hours. Time to recovery varies with the severity of poisoning; in mild cases it may occur within 24 hours and in severe cases complete recovery may take 1–2 weeks, or sometimes longer. Coma can last several days (Paul et al, 1987; Hopper et al, 2002).

The earliest signs of ivermectin toxicosis are usually ataxia, depression, hypersalivation and dilated pupils. There may be vomiting; confusion and disorientation; and sluggish or absent pupil reflexes. There is risk of aspiration pneumonia in animals with hypersalivation and/or vomiting, plus CNS depression.

Severe intoxication is characterised by blindness, tremors, convulsions, hyperaesthesia, hyperreflexia, hypo- or hyperthermia, weakness, coma and paralysis. Bradycardia and respiratory depression can also occur. Sudden-onset blindness

can occur in the absence of severe clinical signs (usually with only dilated pupils and mild drowsiness) in non-susceptible dogs (i.e. those not homozygous for the ABCB1 gene) (Kenny et al, 2008). Ivermectin-induced blindness can last days or weeks, with complete resolution of effects (Kenny et al, 2008).

### Treatment

Depending on the condition of the animal, the amount ingested and the time since ingestion, it may be appropriate to induce vomiting. Repeated dose activated charcoal may be helpful to enhance elimination and prevent reabsorption, as ivermectin is excreted in the faeces.

Management thereafter is supportive, with monitoring of body temperature, hydration status and respiratory function. Oxygen may be required in animals with respiratory depression and nutritional support in those with prolonged coma. Atropine has been used in the management of bradycardia (Heit et al, 1989). Lipid emulsion in recommended, and has been used in numerous cases in companion animals with ivermectin toxicosis (e.g. Clarke et al, 2011; Bates et al, 2013; Epstein and Hollingsworth, 2013; Kidwell et al, 2014; Jourdan et al, 2015; Becker et al, 2017), particularly as benzodiazepines and barbiturates should be avoided as they enhance GABA-mediated inhibitory transmission at GABAa receptors and avermectin drugs enhance the effect of GABA (Snowden et al, 2006) which can prolong recovery. Anaesthetic agents that do not act primarily on GABA receptors should be used instead, such as propofol (Snowden et al, 2006).

## Conclusions

The mechanisms of many of the substances causing neurological effects is unknown. Few have a specific antidote, therefore management in most cases is supportive, with the focus on controlling or preventing seizure activity. Intravenous lipid emulsion can be used in the management of poisoning with a number of common substances causing neurological effects, such as cannabis, tremorgenic mycotoxins, permethrin and ivermectin.

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