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Insecticide Toxicities in Cats

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Insecticide Toxicity in Cats
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Overview
Cats pose a unique set of challenges when exposed to insecticides. Since they are fastidious groomers, any substance applied to their skin will usually result in significant oral exposure as well. Most commonly used emetics are not typically effective in cats, and many insecticides are available in a liquid form, making emesis less likely to be effective. Cats also are more sensitive to substances that require glucuronidation for elimination because their UDP-glucuronosyltransferase is encoded by a pseudogene, resulting in defective glucuronidation.

When treating a suspected insecticide exposure in cats, obtaining an accurate history is critical. It is often useful to have the pet owner bring in the packaging (if available) to determine the active ingredient and concentration of a product. The range of toxicity of insecticides in cats can vary greatly, even within the same chemical class. In Australia, insecticides may also be identified by their APVMA approval number (older products may have an NRA approval number instead), which is required on all insecticide packaging. Other questions to ask a pet owner include how the pet was exposed, if there were other pets exposed (i.e. concentrated permethrin product applied to a dog in the home), when the exposure occurred, if there could have been any prior exposure, onset of clinical signs, and whether the owner attempted any treatment at home.

Initial treatment should involve stabilizing the patient first, particularly if seizures are being seen, followed by decontamination and any appropriate symptomatic treatment. With the exception of acetylcholinesterase inhibitors and amitraz, most other insecticides do not have an antidote available.

Decontamination for insecticide exposure depends on the route of exposure. Cats exposed to products dermally should receive a bath with a mild liquid dish washing detergent, and the person administering the bath should wear gloves to minimize the risk for human exposure. Since cats can become readily chilled after bathing, it is important to keep them warm. For oral exposure, rinsing the mouth out and diluting any ingested substances with milk is recommended. Unless there has been a significant exposure to a highly toxic insecticide, charcoal is rarely recommended. If there has been ocular exposure, the cat’s eyes should be flushed with saline for 20 minutes.
Organophosphates/Carbamates

Organophosphates (OPs) and carbamates competitively inhibit acetylcholinesterase (AChE) by binding to its esteric site. Without AChE, acetylcholine accumulates and causes excessive synaptic neurotransmitter activity. Symptoms of acute exposure to OP or other cholinesterase-inhibiting compounds may include the typical SLUDDE signs (salivation, lacrimation, urination, defecation, dyspnea, and emesis) plus bradycardia, coma, seizures and death.

Pets with organophosphate should be decontaminated and monitored closely for signs. Treatment consists of stabilizing the animal (oxygen, respiratory support) and controlling seizures (diazepam, methocarbamol/guaifenesin, or barbiturates) before proceeding with other treatments. Atropine sulfate is a specific antagonist and may be given (0.1-0.2 mg/kg) to control the muscarinic signs (bradycardia and bronchial secretions). Atropine does not control nicotinic signs. Give 1/4th of the initial dose IV and the rest IM or SQ. The dose can be repeated as needed, but do not over-atropinize the animal. Pralidoxime chloride (2-PAM; Protopam) may also be used for nicotinic signs. 2-PAM interacts with the insecticide-AChE combination and results in the freeing of the AChE and forms a complex with the insecticide that is excretable in the urine. The initial dose is 20 mg/kg IM BID for small animals. If no response after 3 doses, discontinue treatment. Oximes are ineffective once "aging" occurs. However, the time of "aging" varies with the compound and so oximes may be effective even days after exposure.

Muscarinic signs (bradycardia, salivating, vomiting, diarrhea, etc.) can occur for other reasons and so a test dose of atropine can be given to determine whether or not the signs are caused by an anticholinesterase insecticide. Give a pre-anesthetic dose of atropine (0.02 mg/kg IV) and monitor the response. If the heart rate increases and mydriasis occurs, then the muscarinic signs are probably not due to an OP or carbamate insecticide because it usually takes roughly 10X the pre-anesthetic dose to resolve signs caused by insecticides.

AChE activity can be used as diagnostic indicator or a screening test. AChE can be checked in serum, plasma, or whole blood. AChE test results cannot be interpreted without a normal reference from the lab that ran the sample (several different methods of testing with different reference ranges) and because AChE activity varies widely among the different species of animals. If using a human hospital, also send a blood sample from an animal that has not been exposed to an anticholinesterase for at least 8 weeks (human labs will not have established animal reference ranges). Generally, an AChE activity that is <50% of normal indicates significant exposure while an AChE activity <25% of normal plus consistent clinical signs indicates toxicosis. However, blood AChE does not always correlate well with clinical signs, as AChE
activity can remain depressed for 6-8 weeks. Samples that have been refrigerated should be viable for at least one week. On necropsy, AChE activity can be checked in brain or retina. Half of the brain should be submitted to the lab (put the other half in formalin) as AChE activity varies among the regions of the brain (lab will homogenize the half-brain before testing). Animals that die rapidly (in a few hours) are less likely to have depressed brain AChE activity than animals that live longer before dying; however, the blood AChE will probably be depressed (blood-brain barrier). Insecticide screens can also be performed on tissue samples (liver, kidney), source material and GI contents. Samples that are to be shipped or that have to wait longer than 24 hours for testing should be frozen.

**Pyrethrins/Pyrethroids**

Pyrethrins/Pyrethroids bind to the sodium channels on nerves, causing them to remain open and repetitively fire.

**Permethrin**

Permethrin is a synthetic type I pyrethroid. Permethrin is found in shampoos, dips, foggers, spot-ons, and sprays. Permethrins appear to be relatively safe in dogs. Smaller dogs seem to have a greater risk of toxicity and skin hypersensitivity reactions to the spot-ons. Skin reactions can be treated with bathing +/- antihistamines or steroids.

Cats are more sensitive to the toxicity of pyrethroids, because the feline liver is inefficient at glucuronide conjugations relative to other mammalian livers. The low concentration products (sprays, foggers) approved for cats contain 0.05-0.1% of permethrin and do not seem to cause the signs that the concentrated (45-65% permethrin) spot-ons do. Permethrin toxicity usually occurs when the owner applies the dog product to the cat; however, cats which actively groom or engage in close physical contact with recently treated dogs may also be at risk of toxic exposure. Clinical signs of permethrin toxicity in cats include hypersalivation, depression, muscle tremors, vomiting, anorexia, seizures, and possibly death. Onset of clinical signs is usually within a few hours of exposure but may be delayed up to 24 hours. The severity of clinical signs varies with each individual. Treatment recommendations include bathing with liquid dish washing detergent and controlling the tremors. Methocarbamol (50-150 mg/kg IV, do not exceed 330 mg/kg/d) works best to control the tremors. If no injectable methocarbamol is available, the oral form may be dissolved in water and given rectally. Alternatively guaifenesin or intravenous lipid emulsion (1.5 ml/kg bolus followed by 0.25 ml/kg/min CRI for 30-60 minutes) may be
used. If the cat is actively seizuring, barbiturates or inhalant anesthesia may need to be used. Permethrins appear to have no direct action on the liver or kidneys, but fluids may be needed to help protect kidneys from myoglobin break-down products in actively tremoring cats. Prognosis for mildly tremoring cats is usually good, but treatment may last 24-48 hours.

**Avermectins**

In nematodes and arthropods, avermectins bind to glutamate-gated chloride channels causing hyperpolarization by enhancing the movement of chloride ions into the cell. This results in paralysis. In mammals, avermectins cause CNS effects by potentiating the release and binding of GABA receptors in the central nervous system. The most commonly reported clinical signs of toxicosis include depression, weakness, recumbency, ataxia, and coma. Other reported signs include tremors, seizures, transient blindness, bradycardia, and hyperthermia. If the exposure has just occurred and the animal is asymptomatic induce vomiting (if an oral overdose) or consider surgical debridement if given SQ and can localize injection site in massive overdoses. If the animal is symptomatic, treatment is mostly supportive care and repeated dosages of activated charcoal. Activated charcoal/cathartic should be given q 8-12 hours (sorbitol 70% -cathartic of choice) until normal. Treatment can take several weeks (report of one collie in coma for 7 weeks, unpublished report of cat in coma for 18 days). Supportive care is very important (fluids, parenteral nutrition, frequent turning, etc.). Intravenous lipid emulsion could be considered in severe cases as well to shorten the duration of signs, although the effect can be variable. Physostigmine can be given, but it is not an antidote. Physostigmine has a very short beneficial effect (arousal for 30-90 minutes) and should only be used in severely non-responsive dogs (not recommended for cats). The recommended dose is 0.05 mg/kg IM or IV (very slow, over 5 minutes). Prognosis somewhat depends on the speed of onset of clinical signs, the faster the onset, the worst the prognosis.

**Novel Insecticides**

**Fipronil**

Fipronil is a phenylpyrazole insecticide. It is found in spot-ons and sprays (Frontline®) for pets, along with roach traps. It is also licensed for food crops in 30 countries and for use on golf courses in the US. Fipronil works by binding to the GABA receptors of insects and blocking chloride passage. GABA is an inhibitory neurotransmitter in both invertebrates and vertebrates, and it normally stops transmission of impulses. Fipronil causes excitation of the nervous system in insects
by reversing the block caused by GABA. Its neurotoxicity is selective, because the configuration of GABA receptors in mammals is different from insects. The activity of fipronil is opposite to that of ivermectin. Fipronil has a wide margin of safety and can be easily removed by bathing in the first 48 hours after application before it is absorbed into the sebaceous glands. Oral doses equal to 87 pipettes in dogs and 20 pipettes in cats showed no adverse reactions beyond drooling and occasional vomiting. A few skin hypersensitivity reactions have been reported, most likely to the carrier. Fipronil, used off-label, has been reported to cause seizures in rabbits.

**Imidacloprid**

Imidacloprid (Advantage®) is a chloronicotinyl nitroguanide insecticide. It is used for crop, fruit and vegetable pest control, termite control, and flea control in dogs and cats. It works by binding to the acetylcholine receptor on the postsynaptic portion of insect nerve cells, preventing acetylcholine from binding. This prevents transmission of impulses, resulting in death of the insect. There are two binding sites with different affinities for imidacloprid and it may have both agonistic and antagonistic effects on the nicotinic acetylcholine receptor channels. Imidacloprid is a safe compound, although can be found combined with permethrin in certain topical products labeled for use in dogs. It has low toxicity in mammals, because there is a higher concentration of nicotinic acetylcholine receptors in insect nervous tissue than in that of mammals. In addition, imidacloprid has a higher affinity for insect than vertebrate receptors. With oral exposure, salivation or vomiting is occasionally seen and dilution with milk or water is recommended.

**Nitenpyram**

Nitenpyram (Capstar®) is a nitroamines insecticide. It is used as an oral flea adulticide for dogs and cats. It is labeled for use in animals over 4 weeks in age and over 2 pounds in weight. Its mechanism of action is similar to imidacloprid (acts on nicotinic acetylcholine receptor channels). Nitenpyram has a wide safety margin. Some animals become slightly agitated or hyperactive about 15-30 minutes after dosing. This has been attributed to the increased activity of the dying fleas.

**Dinotefuran**

Dinotefuran (Vectra®) is a nitroquanidine, neonicotinoid insecticide. It is an insect synaptic poison. Dinotefuran mimics the action of acetylcholine in the insect, causing repetitive stimulation (tremors, death). Dinotefuran does not bind to mammalian acetylcholine receptor sites. Dermal reactions are possible.
**Spinosad**  
Spinosad (Comfortis®) affects both nicotinic acetylcholine and GABA receptors. It acts at different sites than imidacloprid and avermectins. Imidacloprid and other nicotinic receptor-based insecticides act at a different site than spinosad. Spinosad causes excitation of the insect nervous system, leading to involuntary muscle contractions, prostration with tremors, and paralysis. When spinosad is combined with high dose ivermectin, toxicosis can result. Ataxia and vomiting have been seen at therapeutic doses.

**Amitraz**  
Amitraz (Preventic®) is an alpha-2 adrenergic agonist and can result in pronounced vomiting, ataxia, CNS depression, and cardiovascular signs (typically bradycardia and hypotension). Ileus is also possible. It is rapidly absorbed both orally and dermally, although absorption from collars may be delayed. For decontamination, the collar should be removed and the pet bathed with a liquid dish washing detergent. The mouth should also be rinsed in the event of oral exposure. Atipamezole (50 mcg/kg IM) can be given as a direct antagonist. Yohimbine could also be used, however it has a shorter duration of effect. Atropine should not be given because it can exacerbate GI stasis and increase myocardial oxygen demand.

**Indoxacarb**  
Indoxacarb (Activyl®) is an oxadiazine insecticide that acts by blocking sodium channels in the nervous system of insects. It has a wide margin of safety, with the most commonly reported clinical signs being lethargy, diarrhea, anorexia, and in cats ataxia and depression.

**Hydramethylnon**  
Hydramethylnon is a trifluoromethyl aminohydrazone insecticide that is poorly absorbed in mammals. It inhibits the electron transport system of insects resulting in inactivity, paralysis and death. In companion animals the most common clinical signs are vomiting and gagging, which is typically self-limiting.

**Sulfluramid**  
Sulfluramid is a polyfluorinated sulfonamide found in ant and roach baits. It has a wide margin of safety in mammals. The most commonly reported clinical sign is self-limiting vomiting.
Lufenuron
Lufenuron inhibits chitin formation, preventing molting and maturation of fleas. It has very low mammalian toxicity and can cause vomiting and diarrhea.

Insect Growth Regulators
Insect growth regulators are compounds that mimic insect hormones, typically juvenile hormone. If juvenile hormone concentrations are high, the insect remains in the same stage. Examples of this category include methoprene and pyriproxyfen, both of which have a wide margin of safety in mammals. They may result in dermal hypersensitivity reactions, lethargy, or digestive upset. Tremors are rare, but typically respond to methocarbamol.

Natural Flea Products - Essential oils
D-limonene (derivative of citrus pulp), melaleuca (tea tree oil), pennyroyal and neem oil have all been used to control fleas. Essential oils have minimal to moderate efficacy to control fleas. The most serious toxicological problems occur when an undiluted product is applied directly to the pet. Application of the undiluted product can cause skin and oral irritation, lethargy, vomiting, salivation, ataxia and muscle tremors. Pennyroyal oil has been associated with hepatic necrosis. Cats appear to be more sensitive than dogs to any of the essential oils. Essential oils can penetrate the skin and cause peripheral vasodilation leading to hypotension and hypothermia.
Treatment recommendations include bathing with liquid dish washing detergent, activated charcoal with cathartic, pain control if needed, body temperature regulation and fluids. Most essential oils have long half lives (days) due to entero-hepatic recirculation.