Insecticides: The safe, the not-so-safe, and the downright dangerous
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Organophosphates

Organophosphates (OPs) 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, emesis) plus bradycardia, coma, seizures and death.

With an oral OP exposure and still asymptomatic animal, induce emesis and give activated charcoal. If dermally exposed, wash with a liquid dish soap. Activated charcoal still might provide additional benefit even after a topical exposure. Treatment consists of stabilizing the animal (oxygen, respiratory support) and controlling seizures (diazepam, methocarbamol, 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 (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. Animals do not die from constricted pupils or hypersalivation; the primary goal of atropine use is to control bradycardia and bronchial secretions. Atropine does not affect the AChE-insecticide bond, but blocks the effects of accumulated acetylcholine at the synapse. Pralidoxime chloride (2-PAM; Protopam) may also be used. 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. Oximes are used to control the nicotinic signs. 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 preanesthetic 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 preanesthetic 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 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.

Tetrachlorvinphos

Tetrachlorvinphos (Rabon®) is a low toxicity organophosphate available in collars, powders, dips, sprays, and feed additives. Dogs fed 2000 ppm per day (2 g/kg of food) had decreased plasma cholinesterase activity (normal erythrocyte and brain cholinesterase activity) but no other clinical effects. There have been no reports of delayed neurotoxic effects.

Cats have shown some depression, ataxia and salivation when saturated with the tetrachlorvinphos sprays, but this is due to the alcohol content. Most cats recovered with supportive care (bathing, thermoregulation, etc.).

Disulfoton

Disulfoton is a “hot” organophosphate used in “systemic” rose products. Dogs are usually exposed to these products after the owner mixes them with bone or blood meal to fertilize their roses. Not only can these animals present with the typical SLUDDE signs, but they can also have hemorrhagic diarrhea plus liver and pancreas enzyme elevations.

Onset of clinical signs is 2-8 hours post ingestion. Signs can last for several days (it is believed that there is some enterohepatic recirculation). With disulfoton, do not induce emesis at home if exposure was possibly longer than 30 minutes earlier because of the possibility of acute onset of seizures. If the animal is still asymptomatic, activated charcoal and cathartic may be given. If symptomatic, atropine may be given to control the muscarinic signs. The dose will probably need to be repeated, but do not over-atropinize the animal. 2-PAM may also be used. Use valium, barbiturates or methocarbamol to control seizures and tremors. IV fluids and supportive care as needed. If large amounts of dirt or bone meal are ingested and if the animal does not yet have diarrhea, an enema may help to increase excretion of the product. Prognosis is good to guarded.

Carbamates

Carbamates are also acetylcholinesterase inhibitors but do not “age” like organophosphates.

Carbaryl

Carbaryl is a wide-spectrum carbamate insecticide which is used for insect control on crops and lawns, as well as on poultry, livestock, and pets. It is available as bait,
dusts, wettable powders, granules, dispersions and suspensions. Sevin® dust in a commonly encountered product. Carbaryl is quite safe and rarely causes problems in dogs and cats.

*Methomyl*

Methomyl (Golden Malrin®) is a “hot” carbamate insecticide. It is found in fly baits. These fly baits contain large amounts of sugar that make it very palatable to dogs and other animals. Clinical signs can be seen within 30 minutes of ingestion. Vomiting, seizures are death are the most common. The oral LD50 in the dog is 17 mg/kg.

Do not induce emesis at home due to the quick onset of signs and the possibility for seizures. Treatment consists of atropine, and supportive care to control the seizures. If seizures can be controlled, prognosis is good.

*Pyrethrins*

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

*Permethrin*

Permethrin is a synthetic type I pyrethrin. 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. If the cat is actively seizing, barbiturates or inhalent 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.

*Cyphenothrin*

Cyphenothrin is a synthetic pyrethroid used in several over-the-counter flea spot-on products. It is over-represented in dermal hypersensitivity reactions. Signs and treatment are the same as for permethrin.
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.

Ivermectin

Ivermectin (Heartgard®, Iverheart®, Ivomec®) is derived from the soil fungus, *Streptomyces avermitilis*. Ivermectin is approved for use in cattle, horses, and swine as a parasiticide and in dogs as a heartworm preventative. Ivermectin is only approved for use in cats as an otic drop (Acarexx®), although extra-label use for external parasites has been well documented (200-400 mcg/kg SQ, PO). The half life of ivermectin in the dog is as long as 2-3 days and 90% is excreted unchanged in the feces.

Ivermectin rarely crosses the blood-brain barrier; except in very young animals and sensitive breeds (Collie-type breeds, Australian Shepherd and turtles/tortoises). With the ‘non-sensitive’ breeds of dogs signs may be seen at 2000 mcg/kg, but only 150 mcg/kg is needed in the ‘sensitive’ breeds to cause signs. Cats have demonstrated clinical signs at the “therapeutic dose” of 200 mcg/kg. The most common clinical signs of ivermectin 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.). 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.

If ivermectin is given to a heartworm positive dog or when used as microfilaricide we can see acute anaphylaxis from massive microfilaria die-off. Treat as for any other type of anaphylaxis.

Milbemycin

Milbemycin (Interceptor®, Sentinel®) is a macrolide antibiotic with insecticidal and anthelminthic activity. Milbemycin is labeled as a once a month heartworm preventative/hookworm control agent in dogs and cats and has also been used extra label as a microfilaricide and for the treatment of demodecosis. Half-life in the dog is 40 hours.

Dogs given 2.5 mg/kg demonstrated intermittent ataxia and trembling, young animals were much more susceptible. Signs of prostration and salivation were reported at
7.5 mg/kg. Cats appear to be somewhat more resistant than dogs. Collies that are sensitive to ivermectin may also be sensitive to milbemycin. In a study, 2/5 dogs developed mild depression at 5 mg/kg (10x normal dose), while 10 mg/kg (20x) caused mild depression, mydriasis, hypersalivation, and ataxia within 6 hours. All dogs recovered within 24 hours. Treat the same as ivermectin toxicity.

Milbemycin can cause pale mucous membranes, labored breathing and vomiting, if given to a dog with high numbers of circulating microfilaria. Signs are generally mild and abate in 48 hours.

**Selamectin**

Selamectin (Revolution®) is a novel, semi-synthetic avermectin. Selamectin is rapidly absorbed from the skin into the bloodstream where it protects against heartworm disease, it is then excreted into the intestinal tract where it kills intestinal parasites. Finally, selamectin is selectively distributed from the bloodstream into the sebaceous glands of the skin, forming reservoirs that provide persistent efficacy against fleas, ear mites and sarcoptic mites.

Selamectin is safe in collies and heartworm positive dogs and cats. It has also been used in breeding, pregnant and lactating animals without any adverse effects. Selamectin has been given to six week old puppies and kittens at ten times the normal dose with no problems. With oral dosing, some salivation and vomiting was seen in cats, most likely due to isopropyl alcohol in carrier. In the clinical setting, diarrhea has been reported 24 hours after dosing and is believed to be from the die off of intestinal parasites.

**Moxidectin**

Moxidectin is a semi-synthetic avermectin that is much more lipid soluble than ivermectin. Moxidectin is used as a heartworm preventative in dogs, and as a cattle and horse dewormer. Moxidectin is available as a repository injection (ProHeart®), oral tablets (ProHeart®), pour-on (Cydectin®), and oral gel (Quest®). The route of administration and formulation greatly affects the absorption of the product. Since these products are highly lipophilic, they cross the gut wall rapidly. Therapeutic levels of moxidectin have been measured 30 minutes post oral exposure.

Moxidectin has a wide margin of safety in dogs when given orally. Doses of up to 300 times the therapeutic dose (300 mcg/kg) resulted in little to no side effects. Most problems are encountered when dogs chew on a tube of Quest® or ingest the gel that the horse has spit out. There have been reports of anaphylaxis after ProHeart® injections.

Clinical signs of moxidectin toxicosis and treatment are the same as for other avermectins. Treatment can be needed for an extended time frame due to the long half-life of moxidectin (enterohepatic recirculation). Lipid therapy can be attempted to increase excretion.

**Novel Insecticides**

**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. 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. Results of a chronic feeding study revealed no adverse effects in dogs given imidacloprid at a dose of 15 mg/kg daily for 1 year. Topical application on dogs and cats at a dose of 50 mg/kg also caused no adverse effects. No adverse effects were seen in pregnant and lactating dogs at three times the recommended dose or in pregnant queens at four times the recommended dose. Additionally, 20 times the recommended dose was safe in puppies. Imidacloprid is approved for use in puppies as young as 7 weeks of age and in kittens as young as 8 weeks of age. With oral exposure, salivation or vomiting is occasionally seen and dilution with milk or water is recommended.

**Nitenpyram**
Nitenpyram (Capstar®) is a nitroanilines 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). Once given orally, it is very rapidly absorbed. Peak plasma levels are reached in 1.21 hours for dogs, and 0.63 hours for cats. Half life is 2.8 hours in dogs; and 7.7 hours in cats. Nitenpyram is poorly lipid soluble and has virtually no tissue accumulation. It is rapidly eliminated via the urine unchanged (94%) in less than 24 hours for dogs and less than 72 hours for cats.

Nitenpyram has a wide safety margin. Both dogs and cats were dosed daily with up to 10x the normal oral dose for more than a month without adverse effects. It is safe for pregnant and lactating animals and may be given as often as once daily. 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 nitroanilines, 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.

**Spinosad**
Spinosad (Comfertis®) effects both nicotinic acetylcholine and GABA receptors. It acts at different sites than imidacloprid and avermectins. function that may contribute further to its insect activity. This mode of action is unique. 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 results.
**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.

A study of the skin and hair distribution of fipronil after topical administration revealed that it is widely distributed in the stratum corneum, viable epidermis, and pilosebaceous units. Fipronil is detected on the hair shafts but is never detected in the dermis and adipose tissue, suggesting that it is absorbed and accumulated in the sebaceous glands, from which it is slowly released via follicular ducts.

Fipronil is a safe product. It has been tested and can be used in kittens and puppies as young as 8 weeks of age. It is 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.

**Metaflumizone**

Metaflumizone (ProMeris®) exerts its effects on sodium channels. It blocks these channels and therefore, nerve impulses causing ataxia, paralysis and death in fleas.

**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 toxicologic 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 enterohepatic recirculation.