Ectoparasiticides Used in **Small Animals**

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Overview

- Flea and tick infestation is a major health problem in dogs and cats, and control presents an economic burden to owners.
- Veterinarians are uniquely qualified to explain the host/parasite interrelationships and advise owners on selection of the most suitable control program.
- Active ingredient:
  - All labels should be read carefully for ingredients, age and s
    restrictions, and directions for use.

Macrocyclic Lactones

- Pharmacodynamic
  - they bind to glutamate-gated chloride channels in the parasites' nervous system, increasing their permeability and allowing for the rapid and continued influx of Cl^- into the nerve cell. This inhibits nerve activity and causes paralysis of the parasite.
- Semisynthetic avermectins
  - Selamectin: topical formulations as either a single active ingredient or in combination with sarolaner
  - Ivermectin: topical ear mite medication
  - Eprinomectin: has been combined with fipronil, s-methoprene, and praziquantel
- Semisynthetic milbemycin
  - Milbemycin oxime: ear mite treatment
  - Moxidectin: has been marketed in topical formulations combined with imidacloprid or fluralaner
- These macrocyclic lactones are applied topically, rapidly absorbed through the skin, and distributed via the blood. They have activity against a variety of internal and external parasites.

Cholinesterase Inhibitors

- Pharmacodynamic
  - inhibition of acetylcholinesterase. Insects produce spontaneous muscular contractions followed by paralysis.
- Organophosphates: chlorpyrifos, dichlorvos, malathion, diazinon, phosmet, fenthion, chlorfenvinphos, and cythioate.
- Carbamates: carbaryl and propoxur.
- These compounds were once very popular for their prolonged action and potency.
  - the use of organophosphates has declined because their low margin of safety.
- When these compounds are used for flea or tick control, it should be determined before treatment whether any other cholinesterase inhibitor has been used on the animal or in its environment.

Neonicotinoids

- Nitroquanidines, neonicotinyls, chloronicotines, and recently as chloronicotinyls, that are modeled after natural nicotine
- All neonicotinoids act as agonists on the postsynaptic acetylcholine receptors in insects. This inhibits cholinergic transmission, resulting in paralysis and death.
- Dinotefuran(third-generation neonicotinoid): a topical spot-on with different formulations for dogs and cats. The cat formulation is combined with the insect growth regulator pyriproxyfen and is used primarily to control fleas. The dog formulation contains pyriproxyfen and permethrin and is labeled for control of fleas, ticks, and mosquitoes.

Neonicotinoids

- Imidacloprid: a spot-on topical product and is used primarily to control fleas on both dogs and cats. It has excellent activity against lice.
  - Although it has potent residual activity, it is readily soluble in water, so swimming and repeated bathing may compromise its duration of activity.
- Nitenpyram: Nitenpyram is administered orally in pill form to kill fleas in both dogs and cats. It is absorbed rapidly, with maximal blood concentrations reached within 1.2 hours in dogs and 0.6 hours in cats. Fleas begin to die within 20–30 minutes of administration, with 100% flea mortality within 3–4 hours. The compound is rapidly eliminated, with > 90% excreted in the urine within 24–48 hours, primarily as unchanged nitenpyram.

Formamidines

- Acaricidal compounds has the proposed mode of action of binding to octopamine receptors, a specific group of receptors found in Acari (mites).
- Amitraz: the only approved formamidine in veterinary medicine .
  - It is used primarily as an acaricide to control ticks and mites.
  - The only amitraz-containing product on the market is an amitraz-impregnated collar for control of ticks on dogs.
  - **Amitraz should not be applied to cats in any formulation.**

Oxadiazines

- Oxadiazine insecticides can control a broad spectrum of insects and
- Indoxacarb is the only member of this group currently used in veterinary medicine.
  - It is considered a pro-insecticide that is metabolized within the insect to a more active form, which exerts its effect by blocking the voltage-gated sodium ion channels in insects.
  - Indoxacarb is administered topically in a spot-on formulation for control of fleas on dogs and cats.

Isoxazolines

- Isoxazolines are a new class of compounds that have both potent insecticidal and acaricidal activity. Isoxazolines have a novel mode of action and work as GABA-chloride antagonists, causing overexcitation of the insect and arachnid nervous system and rapid ectoparasite death.
- These external parasiticides have broad-spectrum activity against a wide range of insects, ticks, and mites. They have revolutionized external parasite control and are currently the dominant parasiticide drug class in small animal veterinary medicine worldwide.
- Afoxolaner is available as an oral chewable tablet for dogs, either alone or, in some countries, combined with milbemycin oxime.
- Fluralaner is available in oral formulations for dogs and in topical formulations for dogs and cats. Fluralaner is available as single active ingredient oral chewable tablets and topical formulations combined with moxidectin.

Isoxazolines

- Lotilaner is available in oral tablets for dogs and, in some countries, for cats.
- Sarolaner is available in oral chewable tablets for dogs and in a topical formulation combined with selamectin for cats.
- The compounds are readily absorbed after oral or topical administration and provide 4–12 weeks of insecticide and acaricide activity.

Insect Growth Regulators

- These compounds inhibit the development of immature stages of insects.
  - juvenile hormone mimics (insect growth regulators): Methoprene, fenoxycarb, and pyriproxyfen
  - chitin synthesis inhibitors (insect development inhibitors): Lufenuron (a benzoylphenyl urea)
- These compounds also have ovicidal and embryocidal activity against flea eggs when applied topically to dogs and cats.
- These compounds are active against a wide range of insects, including mosquito larvae;
  - Methoprene is used as a larvicide in the strategic control of mosquito-borne diseases. For flea control, their outdoor use should be limited to specific flea habitats to avoid adverse effects on beneficial insect species.
  - Lufenuron interferes with polymerization and deposition of chitin, killing developing larvae either within the egg or after hatching. Lufenuron is administered orally to dogs or cats or by injection to cats. Female fleas feeding on treated animals are prevented from producing viable eggs or larvae.
  - Diflubenzuron (another chitin inhibitor) and
  - Cyromazine (a molting disruptor)
- They have little or no activity against ticks or other Acari, which undergo incomplete metamorphosis.

Phenylpyrazoles

- These compounds bind to gamma-aminobutyric acid and glutamate-gated receptor sites of insect nervous systems, inhibiting the flux of Cl^- into nerve cells, which results in hyperexcitability.
- These compounds have broad-spectrum activity against fleas, ticks, mites, and lice.
  - Fipronil: numerous fipronil-containing formulations are available worldwide, including an alcohol-based fipronil-only spray, several spot-on formulations that contain only fipronil, a spot-on combination with the insect growth regulator methoprene, and numerous combination formulations that contain fipronil and various pyrethroids. It is very lipophilic; it accumulates in the sebaceous glands, has very low solubility in water, and has prolonged residual activity on both dogs and cats.
  - Pyriprole

Pyrethrins and Pyrethroids

- These compounds rapidly disrupt sodium and potassium ion transport in nerve membranes, resulting in spontaneous depolarizations, augmented neurotransmitter secretion, and neuromuscular blockade, causing paralysis.
- The synergists piperonyl butoxide and *N*-octyl bicycloheptene dicarboximide interfere with the insect detoxification mechanism and can potentiate the activity of pyrethroids.
- Natural pyrethrum is extracted from chrysanthemum flowers and is notable for its rapid but brief action and relative lack of toxicity in dogs and cats.
- Synthetic pyrethroids are pyrethrum-like compounds that generally have greater potency and residual effects but are less well tolerated in cats.
  - Some pyrethroids, such as permethrin, can be highly toxic to cats, resulting in symptoms such as muscle fasciculations and seizures.
- Pyrethroids are generally classified by developmental generation:
  - First-generation pyrethroids are generally unstable in heat and sunlight (eg, allethrin);
  - Second-generation are more potent but not much more photostable (eg, phenothrin and resmethrin);
  - Third-generation are more photostable and more neurologically active isomers obtained by isomeric enrichment (eg, fenvalerate and permethrin),
  - Fourth-generation are more potent and longer lasting (eg, cyfluthrin, cypermethrin, and deltamethrin).
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Spinosyns

- Spinosyns are a novel family of insecticides derived from the fermentation of the actinomycete, Saccharopolyspora spinosa.
- Spinosyns have a novel mode of action, primarily targeting binding sites on nicotinic acetylcholine receptors distinct from other insecticides such as neonicotinoids. Spinosyns also affect gamma-aminobutyric acid receptor function, which may contribute further to their insecticidal activity. These actions cause excitation of the insect nervous system, leading to involuntary muscle contractions, prostration with tremors, and, finally, paralysis.
- The two most abundant products derived from the fermentation process are spinosyns A and D, which are the major active components of spinosad.
  - Spinosad is used to control a wide variety of insects, including flies and fleas.
  - Is formulated as a chewable tablet for dogs and cats. A topical spot-on spinosyn formulation called spinetoram has been developed for cats.

Synergists

- Are generally not considered toxic or insecticidal but are used with insecticides to enhance their activity. They are used primarily to potentiate the activity of pyrethrum or pyrethroids. Synergists inhibit cytochrome P450–dependent monooxygenases or glutathione S-transferases, enzymes produced by microsomes in insect tissues. They bind the oxidative enzymes that would normally break down the insecticide and prevent them from degrading the toxicant.
- Piperonyl butoxide and N-octyl bicycloheptene dicarboxamide are common synergists.

Repellents

- The synthetic pyrethroid permethrin is a rapidly acting neurotoxicant that can cause ticks to leave the host before dying, and may therefore be described as a repellent and not an ectoparasiticide. Various permethrin formulations are labeled as repellents for ticks, mosquitoes, and fleas.
- N,N-diethyl-3-methylbenzamide (DEET, previously called N,N-diethyl-meta-toluamide) remains the most effective currently available insect repellent for humans, but use of DEET in pets has caused weakness, paralysis, liver disease, and seizures. DEET should therefore not be administered to dogs or cats.

Target Parasite Efficacy

- Product labels should be carefully read. Products that contain compounds specifically active against the target parasite should be chosen, whether the concern is fleas, ticks, mites, or a combination of these parasites.
- Duration of activity (ie, "knockdown" or sustained effects) can be the primary concern in product choices. Products should be evaluated based on both their immediate and residual speed of kill. A rapid residual speed of kill is critically important when attempting to manage flea allergy dermatitis and to decrease the chances of a tick transmitting a pathogen.
- Modern parasiticides available for flea and tick control in companion animals provide superior parasite control; however, an understanding of the life cycle of the parasites, along with the mode of action of the particular molecules, is also important. Often, perceived product failures are a result of massive reinfestation from the environment, incorrect product use, or unrealistic expectations.

Toxicity

- Although LD_{50} data concerning the safety or toxicity of an insecticidal product are often helpful, LD_{50} values are not always the best indicator of the safety of specific insecticide formulations applied to pets or premises. The concentration of product (mg/mL), application rate (mg or g/m^2 for environmental products, and mcg or mg/kg for topicals), route of exposure (dermal or oral), total dose, and the species exposed should be considered. The actual risk of exposure during treatment, after treatment, or after accidental ingestion can be assessed only after evaluation of these criteria.
- Because animal toxicity can be modified by formulation technology, active ingredients are not the sole guide to safety assessment of a product. Most commercially available products have undergone adequate safety evaluation for regulatory approval; the label noting such approval remains the best source of information. Cats are sensitive to many insecticides, and caution is needed when using these insecticides on or near cats. Cats in particular can exhibit topical hypersensitivity reactions after parasiticide spot treatment; temporary periods of excessive grooming, hyperesthesia, agitation or subdued behavior can result. Contact dermatitis is rare but can occur in dogs and cats at the site of topical application. Human and environmental safety also should be considered, especially when treating premises, and it should be noted that some compounds may break down into more toxic components when stored for prolonged periods. Formulations generally safe for grass application may induce skin reactions, or even fatal reactions, in sensitive individuals and certain breeds of dogs and cats.

Delivery Systems

- Consumer convenience is an important factor in product choice, especially for flea and tick control. An array of delivery systems has historically been available, including powders, aerosols, sprays, shampoos, rinses, dips, spot-ons, mousses, injectables, oral tablets or liquids, and impregnated collars. However, the safety, efficacy, and ease of use of the newer spot-on and oral application systems have rendered many of the older delivery systems essentially obsolete.
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