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# Novelties in the use of macrocyclic lactones or macrolides endectocides against dog's intestinal nematodes parasites

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The use of Macrocyclic lactones in dogs, for the treatment of intestinal nematodes parasites is very common and has many advantages in the current clinical practice.

These products are similar in that they are antibiotics produced by streptomycete microorganisms and have a large complex of macrocyclic structures.

The macrolide endectoside fall into two major groups, the avermectins and the milbemycins, both of witch are 16-membered macrocyclic lactones.

The avermectins in commercial use are ivermectin, abamectin, selamectin, and doramectin.

Commercially available mylbemycins are, milbemycin oxime and moxidectin.

The macrocyclic lactones (avermectins and milbemycins) are products or chemical derivatives thereof, of soil microorganisms.

The avernectins are fermentation products of *Streptomyces ivermectilis* that have the 16-membered macrocycle replaced by a spirocetal unit at C-17 to C-28, a hexahydrobenzofuran at C-2 to C8a, and a bisoleadrosyloxy disaccharoide at C-13.

The milbemycins fermentation products of *Streptomyces hygroscopicus auerolacrymosus*, are similar to the avermactins but lack the C-13 disaccharide substituient.

The nemadectins, fermentation products of Streptomyces cyaneogriseus noncyanogenus, are classified as milbemycins in that they also lack the disaccharide at C-13, but the nemadectins differ from the milbemycins proper in that they contain a trisubstituited double bond at C-26 in their side chains.

Avermectins include abamectin, ivermectin, selamectin and doramectin.

Milbemycins include milbemycin oxime, and nemadectin include the moxidectin.

MECHANISM OF ACTION. Generally thought that the macrocyclic lactones increased the release of gamma-aminobutiric acid (GABA) from synaptosomes of the nervous system. This, in turn, opened GABA –gated chloride channels. It is now known that these compounds open chloride channels in invertebrates via a specific binding site, glutamate-gated site, apparently occurs in close anatomic proximity to GABA – gated sites, and the macrocyclic lactones may potentiate GABA-gated sites as well (1).

About 50% of the effect of a macrocuclic lactone can be reversed with picrotoxin, a GABA antagonist active at the chloride channel. In nematodes the synapse between interneurons and excitatory motor neurons is the primary site of action, whereas the myoneural junction is the primary site in arthropods. In either case the chloride ion influx lowers cell membrane resistance and causes a slight hyperpolarization of the resting potential of postsynaptic cells. This make neurotransmission more difficult so that transmission of stimuli to muscles is prevented, resulting in a flaccid paralysis of affected parasites followed by death or expulsion (1, 2, 3).

Mammalian GABA-mediated neurotransmission is limited to the CNS and so presumably is the site of action of the macrocyclic lactones.

## IVERMECTIN

CHEMICAL CLASS. The avermectins are a group of chemically related macrocyclic lactones produced by fermentation of the actinomycete Streptomyces a*vermectilis*.

Avermectin is a complex of eight such fermentation products. Four of these are major components (avermectin A1a, A2a, B1a, and B2a) and four minor components recovered in smaller amounts (avermectin A1b, A2b, B 1b, B2b). Of these the B1a component is recovered in greatest amount along with its B1b minor homologue.

Ivermectin, derived from the mixture of B1 avermectins by saturation of the double bond between C-22 and C-23, consists of not less than 80% 22,23-dihydroavermectinB1a and not more than 20% 22,23-dihydroavermctin B1b.

Ivermectin is an off-white powder that is highly lipophilic and hydrophobic.

MECHANISM OF ACTION. It has the mode of action of macrocyclic lactones (1).

Ivermectin is open chloride channels, in invertebrates, binding the glutamate-gated channels in site, near GABA-gated site, which may be also potentiated. Chloride ions cause a slight hyperpolarization of the resting potential postsynaptic cells.

Ivermectin enhances the release of gamma aminobutiric acid at presynaptic neurons. GABA acts as an inhibitory neurotransmitter and blocks the post-synaptic stimulation of the adjacent neuron in nematodes or the muscle fiber of the arthropods.

By stimulating the release of GABA, ivermectin causes paralysis of the parasite and eventual the death (2, 3).

SPECTRUM OF ACTIVITY. In dogs ivermectin is used as a preventative for heartworm, also used as microfilariocide, ectoparasiticide and endoparasiticide (1).

TARGET PARASITES: *Toxocara canis,* Toxascaris leonine, *Ancylostoma, Uncinaria stenocephala* caninum, Trichuris vulpis, Capillaria aerophila, Strongyloides stercoralis, Filaroides osleri, Arthropods Dirofilaria immitis larvae.

Experimental studies indicate that when the drug is used at higher doses it has a wide spectrum of activity. Both 4$^{th}$- stage and adult parasites are eliminated by single SC doses of 0,05 mg/kg *(Ancylostoma caninum, Uncinaria stenocephala)*, 0,1 mg/kg (*Trichuris vulpis*), or 0,2 mg/kg (*Toxocara canis)* SC administration of 0,2 mg/kg is only 69% effective for *Toxascaris leonina*, oral administration at the same dose improves the efficacy to above 95%.

100% reduction in prenatal and transmammary transmission of *Toxocara canis* and *Ancylostoma caninum* from mother to her puppies can be achieved by treating the mothers 10 days before and 10 days after whelping with 0,5mg ivermectin /kg SC each time.

Oral or SC administration at 0,2mg/kg twice, 2 weeks apart, is reported to be 95-100% effective against intestinal stages (but not 3$^{rd}$ –stage parenteral larvae) of *Strongyloides stercoralis* (4).

DOSE. As endoparasiticide:

A) For roundworms, hookworms, or whipworms: 200 µg/kg PO once. Do not use in Collies (5).

B) For treatment of parasitic lung disease (*Capillaria* spp): 0,2 mg/kg PO once (6).

OVERDOSE TOXICITY. In dogs, symptoms of toxicity rarely occur at a single dosage of 2 mg/kg or less. At 2,5 mg/kg mydriasis occurs, and at 5 mg/kg tremors occur. At doses of 10 mg/kg, severe tremors and ataxia are seen.

Deaths occurred when dosages exceeded 40 mg/kg, but the LD50 is 80 mg/kg.

Dogs receiving 0,5 mg/kg PO for 14 weeks developed no signs of toxicity, but at 1-2 mg/kg for the same time period, developed mydriasis and had some weight decreases.

Half of the dogs receiving 2 mg/kg/day for 14 weeks developed symptoms of depression, tremors, ataxia, anorexian and dehydration (4).

The Collie breed appears to be more sensitive to the toxic effects of ivermectin than the other

canine breeds. This may be due to a more permeable blood-brain barrier to the drug or drug accumulation in the CNS of this breed.

The manufactures recommends that ivermectin not be used in foals less than 4 months old, as safety of the drug in animals this young has not been firmly established. However, foals less than 30 days of age have tolerated doses as high as 1mg/kg without symptoms of toxicity.

PHARMACOKINETIC. In dogs up to 95% absorbed after oral administration (4).

While there is a greater bioavailability after SC administration, absorption after oral dosing is more rapid than SC.

Ivermectin is well distributed to most tissues, but does not readily penetrate into the CNS, thereby minimizing its toxicity. Collie breeds apparently allow more ivermectin into CNS than other breeds/species.

Ivermectin has a long terminal half-life in dogs, 2 days.

It is metabolized in the liver via oxidative pathways and is primarily excrated in feces. Less than 5% of the drug as parent compound or metabolites is excreted in the urine.

USE IN PREGNANCY. There was no teratogenesis when ivermectin was administered to pregnant animals at four times the recommended dose (4).

**MILBEMYCIN OXIME**

CHEMICAL CLASS. Milbemycin oxime is a fermentation product of Streptomyces hygroscopicus aureolacrimosus.

Mylbemycin oxime consist of a mixture of not less than 80% A4 milbemycin oxime and not more than 20% A3 milbemycin oxime.

SPECTRUM OF ACTIVITY. Milbemycim oxime, has activity against internal nematodes parasites and external parasites (Demodex canis) (7, 8, 9).

TARGET PARASITES: *Dirofilaria imitis larvae, Toxocara canis, Toxascaris leonina, Ancylostoma caninum, Trichuris vulpis, Demodex canis.*

MECHANISM OF ACTION. Milbemycin oxime acts generally as the others macrocyclic lactones, by disrupting the transmission of the neurotransmitter gamma amino butyric acid (GABA) in dogs.

Milbemycin oxime is open chloride ion channels binding on glutamated-gated channels (anatomically, very near GABA-gated channels) and causes a slight hyperpolarization of the resting potential postsynaptic cells.

PHARMACOKINETIC. After oral administration, approximately 90-95% of the drug passes through the gut, unchanged. The remaining 5-10% is absorbed and subsequently excreted in feces.

DOSE. 0,5 mg/kg body weight.

OVERDOSE TOXICITY. Has been extensively tested with regard to safety. It is no toxic to Collies at up to 20 times the recommended dose and is safe to give to pregnant and nursing puppies (9, 10).

Although an LD50 was never determined for dogs, single oral doses of 200 mg/kg were tolerated in laboratory beagles, and collie dogs tolerated single oral doses of 10 mg/kg without toxicity.

Eight weeks old puppies receiving 2,5 mg/kg (5Xlabel) for 3 consecutive days showed some ataxia and trembling.

Side effects are rare and include depression, lethargy, vomiting, staggering, loss of appetite, diarrhea, seizures, weakness, or excessive salivation.

USE IN PREGNANCY. Studies in pregnant dogs at daily doses 3Xthose labeled showed no adverse effects to offspring or bitch.

Milbemycin does enter maternal milk: at standard doses, no adverse effects have been noted in nursing puppies.

The manufacturer states that at labeled doses the drug is safe to use in puppies as young as 8 weeks old.

## MOXIDECTIN

CHEMICAL CLASS. It is a chemically altered product of Streptomyces aureolacrimosus noncyanogenus.

Moxidectin has produced by chemical modification of nemadectin, the principal component of the LL-F28249 antibiotic complex produced by Streptomyces cyaneogriseus noncyanogenus. Unlike ivermectin, abamectin , and milbemycin oxime, moxidectin is essentially a single compound rather than a mixture of two closely related compounds.

SPECTRUM OF ACTIVITY. Moxidectin is an endectocide, with activity against nematodes internal parasites and arthropods external parasites

TARGET PARASITES: *Dirofilaria immitis larvae, Ancylostoma caminum, Uncinaria stenocephala, Toxocara canis, Toxascaris leonina.*

Moxidectin is effective against larvae of *Dirofilaria immitis* (11, 12, 13).

Is effective against *Ancylostoma caninum* at 0,025 mg/kg and against *Uncinaria stenocephala* at 0,15 mg/kg.

It has also good activity against *Toxocara canis* and *Toxascaris leonina* at the doses tested (0,025 to 0,3 mg/kg orally) (14, 15).

A single oral dose of 25 µg/kg will remove the former hookworm, but a dose of at least 150 µg/kg is necessary for similar efficacy against the latter.

Whipworms are not controlled by doses up to 300 µg/kg (15).

Moxidectin is an effective heartworm prophylactic at a remarkably low doses. Is effective 100% against both 1st and 2nd –month-old larvae of *Dirofilaria immitis* at dose of 3,0 µmk/kg (14).

MECHANISM OF ACTION. The same as the others macrocyclic lactones (Acts by opening the chloride ions channels binding the glutamate-gated site and the near GABA-gated site, causes a slight hyperpolarization of the resting potential postsynaptic cells.)

PHARMACOKINETICS. Moxidectin is even more lipophilic and hydrophobic than ivermectin, and has a result, therapeutically effective tissue levels persist somewhat longer. Like ivermectin, moxidectin is excreted mainly in feces.

DOSE: 0,5 mg/kg or less.

OVERDOSE TOXICITY. It is very safe and at the recommended dose it is safe in rough-coated collies (14, 16), and it produced no adverse effects in collie dogs when given at 20 times the approved dose, although mild toxic effects were seen at 30 times the approved dose (15).

USE IN PREGNANCY. Moxidectin, is safe, in breeding animals.

## SELAMECTIN

CHEMICAL CLASS. It is produced as a fermentation product of Streptomyces avermetilis which is then chemically modified (17, 18).

Selamectin is a modified avermectin with the chemical name (5Z,25S)-25-cyclohexyl-4-0-de(2,6-dideoxy-3-0-methyl-abino-hexopyranosy1)-5-demothexy-25-de(1-methylpropyl)-22,23-dihydro-5-hydroxyminoavermectin A1a.

MECHANISM OF ACTION. Selamectin increased the release of gama-aminobutiric acid (GABA) from the synaptosomes of the nervous system. This, in turn, opened GABA-gated chloride channels.

Selamectin, like the others macrocyclic lactones bind selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells.

Selamectin causes hyperpolarization of the resting potential postsynaptic cells.

PHARMAKOCINETICS. The topical bioavailability in dogs is only 4%. The terminal half-life is longer after topically administration than after intravenous, which suggest sustained

release from an extravascular depot. The half-life after topically administration is 11 days.

SPECTRUM OF ACTIVITY. It has activity against nematodes and arthropods (17, 18).

TARGET PARASITES: *Toxocara canis, Toxascaris leonina, Ancylostoma caninum, Uncinaria stenocephala, Dirofilaria immitis larvae, Ctenocephalides spp.*

DOSE. The approved topical dose is minimum of 6,2mg/kg for dogs.

OVERDOSE TOXICITY. The safety of selamectin was evaluated by treating puppies with up to 114mg/kg at 28-dayintervals for a total of seven treatments. No adverse reactions were observed.

The drug was administered at 10 times the recommended dose, and no undesirable effects were observed.

The drug was administered at 3 times the recommended dose to dogs infected with adult heartworms and no undesirable effects were observed.

The drug was also administered at 3 times the recommended dose in breeding male and female dogs, including pregnant and lactating females nursing their litters at 5 times the recommended dose to ivermectin sensitive collies-dogs, and no undesirable effects were observed.

USE IN PREGNANCY. Is safe for use in breeding dogs (17, 18).

CONTRA-INDICATIONS. Do not use in dogs under 6 weeks age.

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