Evaluation of efficacy of selamectin, fipronil, and imidacloprid against *Ctenocephalides felis* in dogs

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Objective—To evaluate efficacy of monthly administration of selamectin, fipronil, and imidacloprid against *Ctenocephalides felis* in dogs.

Design—Randomized controlled trial.

Animals—44 healthy dogs.

Procedure—Dogs known to be free of fleas were infested with 100 unfed adult fleas on days –28 and –21. On days 0, 30, 60, 90, and 120, dogs (12/group) were treated by topical administration of selamectin (6 mg/kg [2.7 mg/lb] of body weight), fipronil (7.5 mg/kg [3.4 mg/lb]), or imidacloprid (10 mg/kg [4.5 mg/lb]); 8 untreated dogs were used as controls. On day –6 and every 2 weeks after initial treatment, comb counts of viable adult fleas were made, and fleas (≤ 50/dog) were replaced onto the dog from which they were removed. On day 89, fleas were not replaced. On day 91 and every 7 days until the end of the study, dogs were challenged with 20 adult fleas.

Results—14 days after initial treatment, geometric mean flea counts were reduced by 97.5 to 99.1% for all treatments, compared with pretreatment counts on day –6. Selamectin, fipronil, and imidacloprid reduced geometric mean flea counts by 99.7 to 100% from day 29 to the end of the study.

Conclusions and Clinical Relevance—Selamectin is as effective as fipronil and imidacloprid in reducing *C felis* infestation in dogs housed for 3 months in a flea-infested environment under conditions known to support the flea life cycle, and in protecting against subsequent weekly challenges with *C felis* for an additional 2 months. (*J Am Vet Med Assoc* 2000;217: 1669–1671)

Avermectins are closely related, complex 16-membered macrocyclic lactones produced naturally as fermentation by-products by the actinomycete *Streptomyces avermitilis*.[1] They are potent anthelmintics. Naturally found avermectins and their derivatives are effective against gastrointestinal tract parasites in numerous species, including sheep,[2] gerbils,[3] cattle,[4,5] and horses.[6] They have also been used against endoparasites in cats and dogs.[7] In addition, avermectins are efficacious against some ectoparasites of several species.[8-10] The mechanism of action of avermectin compounds in these effects has remained elusive; 1 action appears to be an increase in membrane permeability to chloride ions through interaction within **gamma-aminobutyric acid (GABA)** binding sites.[11]

Selamectin is a novel semisynthetic derivative of an avermectin and was discovered and developed for use specifically in dogs and cats as a topical parasiticide. The purpose of the study reported here was to compare the efficacy of monthly administration of this new avermectin against *Ctenocephalides felis* in dogs with that of fipronil and imidacloprid.

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Materials and Methods

Dogs—The study included 22 male and 22 female 1- to 6-year old Beagles that weighed 10 to 25 kg (22 to 55 lb). Dogs were fed once daily with a maintenance ration of commercial dog food and allowed access to water ad libitum. All dogs were reared indoors from birth and vaccinated against *Bordetella bronchiseptica,* canine parvovirus, canine distemper virus, canine adenovirus, leptospirosis, coronavirus, and parainfluenza virus during the period from 1 year to 20 days prior to initiation of the study. Dogs were not treated with ectoparasiticides or avermectin drugs for at least 60 days prior to the first experimental infestation with fleas.

Daily general health observations were made for each dog. Physical examinations were conducted by a veterinarian on day –31, on each day of treatment, and on each day following treatment.

Animal housing—Pens were contained in a single room controlled for temperature, humidity, and ventilation. Dogs were housed individually in 2.0 × 0.88-m pens that were separated by stainless steel walls 1.85 m high. Raised sisal-carpeted sleeping areas were provided in each pen and were changed before fleas were applied for the first part of the study.

Separate coveralls and gloves were used by investigators who entered pens for each of the treatment groups. Additionally, to avoid transfer of fleas, investigators changed overboots between pens.

Pharmaceuticals and initial infestation—Fipronil[a] and imidacloprid[b] are available commercially. Fipronil was administered topically as a 9.7% solution in the commercial unit dose to approximate a dose rate of 7.5 mg/kg (3.4 mg/lb) of body weight. Imidacloprid (9.1% solution) was administered topically to approximate a dose rate of 10 mg/kg (4.5 mg/lb; 2.5 ml).

Selamectin[c] is available commercially. It was prepared as a 12% solution in glycol ether and isopropyl alcohol. It was administered in a unit dose to provide a minimum dose rate of 6 mg/kg (2.7 mg/lb).

Adult fleas (*C felis*) were raised and provided in vials within a few days of hatching by the same laboratory that conducted the study. On receipt, fleas were inspected for viability and were counted within vials to reconfirm the number of fleas in the vial. Approximately half of the fleas in each vial were males. Flea viability was assessed visually prior to placement of the fleas on the dogs. Vials of fleas were warmed by holding in a hand for 10 minutes and then examined. Any fleas that were unable to maintain a normal posture or jump were replaced before placing the fleas on dogs.

Experimental design and procedures—The study compared 3 treatments by using a mixed-model repeated-mea-

sures design in a single study composed of 2 parts. The first part tested the treatments against established flea infestation for 3 months. The second part tested treatments against weekly challenge with fleas for 2 months.

Selection for study—On day –40, dogs were combed free of fleas and moved to clean noninfested housing. Combing was performed by investigators who used a separate fine-tooth comb for each dog. Investigators were unaware of treatment allocation. Combing was conducted in single strokes for at least 15 minutes and continued until 5 minutes after the last flea was found. Dogs were combed again on day –39 to ensure that they were free of fleas, then infested with 100 viable unfed adult fleas. Fleas were applied to each dog by parting the hair in the dorsal lumbosacral area and turning the uncapped warmed vial of fleas upside down in the parted hair, allowing the fleas to disperse into the hair. On day –36, 72 hours after infestation on day –39, dogs were combed, and the fleas collected from the combing were counted and removed. Technicians who performed the comb counts were unaware of treatment assignments. Dogs were selected for the study on the basis of retention of a flea burden, as assessed by results of flea counts performed on day –36 and satisfactory results of physical examinations performed on day –31. In addition, 8 nontreated dogs (4 males, 4 females) with typical flea burdens were selected to act as sentinels. Nontreated dogs (sentinels) were housed in pens that were interspersed at approximately equal intervals between the pens that housed treated dogs.

Chronic infestation and assignment to treatments—Infestations were established prior to treatment by placing 100 viable unfed adult fleas on each dog on day –28 and again on day –21. On day –6, flea counts were conducted, and collected fleas were placed in covered glass jars. Fleas were then replaced on the dogs from which they were removed, up to a maximum of 50 fleas, to aid in the maintenance of the infestation. Dogs were randomly assigned to treatments on the basis of sex and stratified counts of fleas made on day –6. Treatments (selamectin, fipronil, or imidacloprid) were administered on days 0, 30, 60, 90, and 120. Selamectin was applied at a single site to the skin of each dog's back at the base of the neck in front of the scapulae. Fipronil and imidacloprid were applied, according to label instructions. Fleas were counted and replaced, up to a maximum of 50 fleas, on days 14, 29, 44, 59, and 74. On day 89, fleas were counted but not replaced. Nontreated sentinel dogs were combed free of fleas whenever excessive flea burdens were detected.

Flea challenges—Twenty unfed adult fleas were applied to each dog on days 91, 98, 105, 112, 119, 126, 133, 140, and 147 of the study. Fleas were counted and replaced on days 94, 101, 108, 115, 122, 129, 136, and 143. The study concluded on day 150 when fleas were counted and not replaced.

Statistical analyses—Flea counts were analyzed by use of a mixed-model repeated-measures ANOVA of ln (count + 1).[12] Pairwise comparisons among treatments were made for each data collection time point by use of the Fisher protected least significant difference. Geometric means, calculated by back-transforming the least-squares means, were used to estimate the percentage reductions in flea counts at each time point within all treatment groups, according to the formula:

$$\% \text{ reduction} = ([\text{geometric mean, day } -6] - [\text{geometric mean, day } X)] \times 100) / (\text{geometric mean, day } -6).$$

For comparisons of counts before (day –6) and after treatments and among groups, $P \leq 0.05$ was considered significant.

Results

Flea infestations resulted in geometric mean flea counts that were not different among treatment groups prior to the initiation of treatments on day 0. Fourteen days after the first treatment, flea counts were reduced in all groups, compared with pretreatment mean values (**Table 1**). Mean flea count of the fipronil-treated group was reduced by 99.1% on day 14 and was significantly lower than that of the imidacloprid and selamectin groups, which were reduced by 97.8 and 97.5%, respectively. All treatment groups had mean flea counts for days 29 through 150 that were reduced by 99.7 to 100%, compared with their respective pretreatment flea counts, and that did not differ significantly among groups.

Table 1—Percentage reductions in geometric mean flea counts for *Ctenocephalides felis*-infested dogs (n = 12/group) treated with selamectin, fipronil, or imidocloprid on days 0, 30, 60, 90, and 120. Dogs were infested with 100 fleas on days −28 and −21; these fleas were removed on day 89. Dogs were reinfested with 20 fleas/d on days 91, 98, 105, 112, 119, 126, 133, 140, and 147

Day of study	Selamectin	Fipronil	Imidacloprid
−6	0.00	0.00	0.00
14	97.47	99.13	97.79
29	99.89	99.93	99.74
44	99.93	100.00	99.94
59	99.88	99.91	99.93
74	100.00	100.00	100.00
89	99.94	100.00	99.92
94	100.00	100.00	100.00
101	99.97	100.00	100.00
108	100.00	100.00	100.00
115	100.00	100.00	100.00
122	100.00	100.00	100.00
129	100.00	100.00	100.00
136	100.00	100.00	99.98
143	99.98	100.00	100.00
150	100.00	100.00	100.00

The nontreated sentinels had flea counts that indicated housing and environmental conditions were able to support a chronic increasing flea burden after infestation. In consideration of their welfare, sentinels were combed free of fleas, without replacement, whenever the dogs appeared uncomfortable because of the flea burden. Therefore, no direct comparisons were made between treatment groups and sentinels.

No inflammation at the treatment site, mydriasis, vomiting, lethargy, tremors, hyperactivity, convulsions, excessive salivation, or other abnormal clinical signs were seen in any of the treatment groups during the study. Alopecia was not observed in any treatment group before day 0. After day 0, hair loss was observed in the treatment groups with incidence that ranged from 0.4 to 1.0%. Among the sentinels, alopecia was observed with an incidence of 6.0%.

Discussion

Results of the study reported here indicated that selamectin was as efficacious as imidacloprid and fipronil in reducing flea burdens in experimental infestations with *C felis* in dogs. Strategies for the control of flea infestations in dogs have focused on disruptions of the flea life cycle at several stages. Lufenuron, a benzoyl-urea compound, is an inhibitor of chitin synthesis; it disrupts the flea life cycle by interfering with the development of flea eggs[13,14] but has no effect on adult fleas. Selamectin, fipronil, and imidacloprid are adulticidal compounds that disrupt the flea life cycle by killing adult fleas before eggs are laid. Fipronil, a

phenylpyrazole, is a known GABA inhibitor,[15] but it is not known whether this is the mechanism responsible for its parasiticidal activity. Imidacloprid is a chloronicotinyl nitroguanidine that depolarizes postsynaptic nicotine receptors in insects.[16] Findings in other studies[17,18] that evaluated imidacloprid agree with the results reported here and indicate nearly complete relief from experimental flea burdens. Arther et al[17] measured a 98 to 100% reduction in flea counts on imidacloprid-treated dogs (compared with untreated controls) during 34 days of study. Hopkins et al[18] also found that 10 mg of imidacloprid/kg reduced the burdens of weekly flea challenges to dogs by 100% the first week after treatment but by only 95% the fourth week after treatment.

During the 150-day period after initial treatment in the study reported here, fewer observations of alopecia were recorded for the treated groups, compared with the group of nontreated dogs. However, statistical analysis was not performed on the observations, and definitive statements with regard to hair loss within and among treatments may not be drawn.

Selamectin, like other adulticides, caused an immediate reduction in flea burdens and had nearly complete effectiveness (geometric means ≤ 0) against fleas during the 150-day study. The efficacy of selamectin may also be attributable in part to effects at other stages in the flea life cycle. McTier et al[19] demonstrated that selamectin was 98.8 to 99.8% effective in reducing the number of flea eggs produced for 30 days following treatment. They also reported that of the eggs collected from selamectin-treated dogs and cats, there was a 95 to 100% reduction in the proportion of eggs that developed into larvae or adults, indicating ovicidal activity.

All 3 compounds provided excellent flea control under conditions that supported the flea life-cycle during the laboratory study reported here. These compounds rapidly eliminated the flea infestations that were established prior to treatment and prevented the establishment of further infestations when dogs were challenged weekly with additional fleas.

[a]Frontline Top-Spot, Merial Animal Health Ltd, Harlow, UK.
[b]Advantage, Bayer Animal Health, Bury St Edmunds, UK.
[c]Revolution, Pfizer Inc, New York, NY.

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