Control of Fleas on Dogs and Cats and in Homes with the Combination of Oral Lufenuron and Nitenpyram*

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ABSTRACT

Efficacy of lufenuron (Program®, Novartis Animal Health, Greensboro, NC), an insect growth regulator, and nitenpyram (Capstar™, Novartis Animal Health), an insecticide for reducing flea populations, was evaluated in 35 flea-infested dogs and cats residing in 18 households in Tampa, Florida. Pets were randomly allocated by household to two treatment groups. Pets in both treatment groups were given lufenuron orally according to label directions on Day 0, then once a month for 3 months. Pets in one group were also given nitenpyram tablets by the owner orally once a day every other day. Pets in the second group were given nitenpyram by their owners as needed but no more frequently than once daily. Flea numbers on pets and in homes were assessed throughout the study by the use of visual body area counts and intermittent-light traps, respectively. The combination of lufenuron and nitenpyram reduced flea populations on pets by at least 97.3% within 7 days and maintained this rate of reduction in flea numbers for the duration of the study, regardless of which regimen was used for administering nitenpyram. For either group, premise flea counts were reduced by up to 89.5% by Day 28 and by as much as 100% by Days 84 to 90.

INTRODUCTION

Effective killing of fleas is necessary to alleviate pet discomfort and provide client satisfaction. Flea control is achieved by eliminating adult fleas on pets and by preventing future flea generations. Although these fundamental goals have changed little in the past 15 years, the strategies used to achieve them continue to
evolve. For many years, flea development in the home was prevented by application of insecticides in the premises. Products containing compounds such as pyrethrins, carbaryl, lindane, dichlorvos, phosmet, and chlorpyriphos were used both in the environment and on the pet. Cythioate, available in tablet and liquid formulations for oral administration, was used widely, but its efficacy in both dogs and cats was variable. Applications of insecticide sprays, shampoos, and dips to dogs and cats in conjunction with environmental treatments have been (and still are) recommended, but these treatments have often been problematic for many pet owners.

The development of spot-on insecticide formulations has greatly facilitated flea control, offering pet owners ease of application and prolonged residual activity. In one study, a spot-on formulation of permethrin provided greater than 95% efficacy for 22 days against flea populations on dogs. A fenthion spot-on formulation applied to dogs at 20 mg/kg provided 100% control at 17 days and 93.5% control at 21 days. A 10% spot-on formulation of imidacloprid was 95.1% to 97.8% effective in killing fleas on dogs and cats for at least 4 weeks. In addition, applications of fipronil in a 10% spot-on formulation every 28 days provided 100% control of fleas on cats for 168 days.

Pet owners and veterinarians have increasingly relied on these spot-on topical insecticides to control fleas on pets. Although the safety record of most of these compounds is excellent, the changing attitude of society toward insecticides has led to compliance problems and use of questionable alternative therapies such as ultrasonic flea collars, brewers yeast, and elemental sulfur.

Flea development now can be interrupted effectively at the host level with the use of insect growth regulators, which are classified as either topical juvenile hormone analogs or systemic chitin synthesis inhibitors. Topical or oral administration of these compounds prevents viable reproduction by causing the death of developing larvae either within the egg or shortly after hatching. One such insect growth regulator available for cats and dogs is lufenuron (Program®, Novartis Animal Health, Greensboro, NC). Although these compounds effectively prevent flea development, they do little to impact emerging fleas or those already feeding on their hosts. Therefore, concurrent use of an adulticide is still recommended for adequate control of existing flea infestations.

Nitenpyram (Capstar™, Novartis Animal Health), a neonicotinoid, is a new systemically active, orally administered insecticide that has demonstrated activity against a variety of sucking insects, including aphids, thrips, white flies, and leafhoppers. When administered orally to dogs and cats, nitenpyram is rapidly absorbed and eliminated. Maximum blood levels are reached within 1.2 hours in fasting dogs and 0.6 hours in cats. The half-life of the drug is reported to be 2.8 hours in dogs and 7.7 hours in cats. When nitenpyram was administered orally to flea-infested dogs and cats, more than 99% of the fleas were dead with 4 to 6 hours.

The objective of the present study was to determine the efficacy of the oral insecticide, nitenpyram, and the insect growth regulator, lufenuron, when used in combination for controlling flea infestations in naturally infested households in Tampa, Florida.

MATERIALS AND METHODS

Participating Households

Eighteen flea-infested homes in and around Tampa, Florida were included in the study. Participating households fulfilled the following criteria: One to four healthy, nonfractious dogs and/or cats lived at the residence; a minimum of five adult fleas were collected in two lighted flea traps during a 16- to 24-hour period; a
minimum of five adult fleas were observed on at least one dog or cat; and owners were willing to start the study between May 20 and June 15 and to participate in the study for 90 days.

**Animals**

There were 25 dogs and 10 cats in the 18 households. Dogs ranged in age from 4 months to 11.5 years and weighed from 3.6 to 45.4 kg. Cats were between 1 and 8 years of age and weighed 2.3 to 5.9 kg each.

**Allocation and Treatment**

A few weeks prior to the initiation of the study, advertisements were placed in Tampa newspapers soliciting participants for a research project to evaluate flea products. Pet owners contacted the participating animal hospital for prescreening as to numbers of pets in households, animal disposition, and presence of fleas. A research team traveled to each pet owner’s home starting May 20. As each home qualified for the study based on the acceptance criteria, they were randomly allocated to one of two treatment groups. The last home was placed in the study on June 15.

There were 10 households in Group 1 and eight in Group 2. Pets were weighed on Day 0 to ensure proper dosing. Pet owners were given the monthly dose of lufenuron for each pet in the household and were instructed to administer the drug orally with a meal according to label directions. Lufenuron was redosed every 28 to 30 days for a total of three treatments.

Pet owners in both study groups also received a supply of nitenpyram tablets at the start of their participation. All pets in Group 1 were given a nitenpyram tablet by their owners every other day for the duration of the study. Pets weighing less than 11.4 kg received one 11.4-mg tablet; pets weighing more than 11.4 kg received one 57-mg tablet. Nitenpyram was administered to pets in Group 2 by their owners as needed but no more than once daily. Frequency of administration in this group was at each pet owner’s discretion based on individual perceptions of flea burdens and pet distress. Members of the research team returned to each home for follow-up evaluations and to retrieve treatment containers to verify treatments had been given. No other topical or premises flea treatments were used during the study. No restrictions were placed on animals regarding exposure to rain, swimming, bathing, or movement outdoors.

**Flea Population Assessment Techniques**

Numbers of fleas on pets were assessed at their home, using a visual body area count method on Days 0, 7, 14, 21, 28, 40 to 45, 54 to 60, 69 to 75, and 84 to 90. Counts for all participating pets were performed by the same two research team members who had received prior training in this evaluation procedure. Body area counts were performed by parting the hair at the dorsal midline, tail head, left lateral thorax (point of elbow to last rib), right lateral thorax, and inguinal region of each animal and counting visible fleas for up to 1 minute at each location. Pet owners were instructed that nitenpyram was not to be administered within 24 hours of a scheduled evaluation.

Numbers of adult fleas in homes were determined using intermittent-light flea traps on the same day that flea numbers on the pets were assessed. One trap was placed in each of two rooms for 16 to 24 hours; room selection was based on time spent in the room by pets or by owner observation of fleas in the room. Traps were placed in the same location in those rooms at each counting period. Total numbers of fleas collected in both traps were recorded, and the species of fleas trapped were determined by inspecting trapped fleas under a dissecting microscope.
Counts of fleas on all animals within a treatment group were combined, giving a total “pet flea count” for each treatment. Because count data for pets and premises are skewed with a long right tail, the data were transformed to the natural logarithm of (count + 1) to calculate geometric means. Percentage control achieved by the flea products at each day of evaluation (Day X) was calculated by the following formula:

\[
\% \text{ Control} = \frac{(\text{Day 0 geometric mean count} \ - \ \text{Day X geometric mean count})}{\text{Day 0 geometric mean count}} \times 100
\]

The pet and trap counts were analyzed separately at each time point, using the Wilcoxon rank sum test (also known as the Mann-Whitney test) to test for differences in the two groups.

### RESULTS

#### Treatments

The mean dosage rate of lufenuron administered monthly was similar for pets in the two treatment groups. Cats in Group 1 received lufenuron at 40.7 ± 11.7 mg/kg and dogs received 16.4 ± 2.2 mg/kg. In Group 2, the mean dosage rate was 37.8 ± 11.8 mg/kg for cats and 16.0 ± 6.2 mg/kg for dogs.

Nitenpyram was administered at 2.2 ± 0.7 mg/kg to pets in households assigned to Group 1 and 1.9 ± 0.8 mg/kg for those in Group 2. Pets in Group 1 received a nitenpyram tablet 15 times during the first 28 days (as scheduled) and continued to receive tablets every other day for the duration of the study. A mean of 12.3 tablets (range = 3 to 27) were administered to each pet in Group 2 during the first 28 days of the study; administration of tablets decreased sharply in this group during Days 28 to 90; on the average, only 4.7 tablets (range = 0 to 10) were given in each household during that 62-day period.

#### Fleas on Pets

On Day 0, the geometric mean number of fleas was 15.8 (range = 5 to 51) per animal in Group 1 and 19.2 (range = 8 to 125) per animal in Group 2 (Table 1). For both treatment pro-

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### TABLE 1. Reduction in Flea Counts When Naturally Flea-Infested Dogs and Cats in 18 Homes in Tampa, Florida were Treated with Lufenuron and Nitenpyram

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Dogs</th>
<th>Number of Cats</th>
<th>Days After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  7  14  21  28  40–45  54–60  84–90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lufenuron monthly/ nitenpyram every other day</td>
<td>15  5</td>
<td>15.8  0.4  0.3  0.4  0.3  0.0  0.1  0.0</td>
<td>(97.3) (97.9) (97.5) (98.4) (100) (99.5) (100)</td>
</tr>
<tr>
<td>Lufenuron monthly/ nitenpyram as needed†</td>
<td>10  5</td>
<td>19.2  0.5  0.4  0.4  0.2  0.3  0.0  0.0</td>
<td>(97.5) (97.9) (97.9) (99.2) (98.5) (100) (100)</td>
</tr>
</tbody>
</table>

*% Control = \(\frac{(\text{Day 0 geometric mean count} \ - \ \text{Day X geometric mean count})}{\text{Day 0 geometric mean count}} \times 100\)

†Administered by owners as needed but no more frequently than once daily.
grams, flea numbers on pets were reduced by 97.3% or better at all counting times after Day 0. Counts in both groups were reduced by 100% on Days 84 through 90. There were no significant differences in animal flea counts between the two groups at any evaluation ($P > .05$).

No relationship was detected between numbers of fleas present on an animal and the frequency with which nitenpyram was administered in Group 2. Three dogs in two separate homes, with average initial counts of 8.3 fleas, were given nitenpyram tablets every 1.1 days by their owners during the first month of the study. The pet owner whose home had the highest initial trap count (499 fleas) and whose dog had the highest pretreatment flea count (125 or more) administered nitenpyram every 2.3 days.

### Fleas in the Premises

During the entire 90-day study, 3037 fleas were trapped in the 18 residences. All fleas were identified as *Ctenocephalides felis*, the cat flea. On Day 0, a mean of 8.3 (range = 5 to 36) and 16.6 (range = 5 to 499) fleas were trapped in Group 1 and 2 homes, respectively (Table 2).

In all households, regardless of the nitenpyram treatment schedule, numbers of adult fleas collected in traps decreased minimally during the first 2 weeks of the study. However, numbers of fleas trapped on Day 28 were reduced by 89.5% in Group 1 and 86.4% in Group 2 (Table 2). Although numbers of fleas collected in traps gradually declined over the first 3 weeks of the study, considerable variability occurred among individual homes. In one home in each group, substantially more fleas were collected from the premises at follow-up evaluations than on Day 0. In one home in Group 1, the trap count increased from 11 on Day 0 to 42 on Day 21; and in a home in Group 2, the trap count increased from 499 on Day 0 to 894 on Day 14. Nevertheless, the combination of lufenuron given monthly and nitenpyram administered every other day reduced numbers of fleas captured in light traps by 100% in homes in Group 1 on Days 40 through 45 and 98.7% on Days 84 through 90 (Table 2). In Group 2, light-trap flea counts were reduced by 96.4% and 100% on Days 40 through 45 and 84 through 90, respectively. At no time were the trap counts of the two treatment groups significantly different ($P > .05$).

### TABLE 2. Reduction in Flea Counts in 18 Homes in Tampa, Florida When Naturally Flea-Infested Dogs and Cats were Treated with Lufenuron and Nitenpyram

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Homes</th>
<th>Geometric Mean Fleas Counts (% Control*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Lufenuron monthly/ nitenpyram every other day</td>
<td>10</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(52.5)</td>
</tr>
<tr>
<td>Lufenuron monthly/ nitenpyram as needed†</td>
<td>8</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(33.6)</td>
</tr>
</tbody>
</table>

*% Control = ($\frac{\text{Day 0 geometric mean count} – \text{Day X geometric mean count}}{\text{Day 0 geometric mean count}} \times 100$)

†Administered by owners as needed but no more frequently than once daily.
Lufenuron is a chitin synthesis inhibitor that prevents development of flea populations by inhibiting development of flea larvae either before or after hatch but does not have any significant adulticidal activity. Therefore, during the initial 21 days of the study, reductions in visual body area counts on the pets were directly attributable to the adulticidal action of nitenpyram.

The flea count methodology used in this study has been shown to detect an average of 23.5% of the pet flea burden. Therefore, actual initial geometric mean flea burdens were estimated to be 67 for pets in Group 1 and 81.7 for pets in Group 2. The high levels of flea control observed on pets in both groups from Days 7 through 21 demonstrates that nitenpyram was effective in killing adult fleas. This adulticidal activity was evident even though large numbers of fleas were emerging in the homes and causing continual reinestation.

The pet owners in Group 2, who were instructed to administer nitenpyram “as needed,” administered one tablet on average every 2.3 days during the first 28 days, similar to the prescribed administration schedule of one tablet every 2 days. These pet owners could have administered the tablets as often as once a day, but most found they obtained satisfactory results giving the tablets every other day. Although the half-life of nitenpyram in dogs and cats is reported to be 2.8 and 7.7 hours, respectively, administration of the compound every 2 days provided substantial reductions in flea populations.

The intermittent-light flea traps used in this study have a green-yellow filter with a transmittance spectrum centered at 515 nm and 82.5-nm half-height width and a 10-minute on/5-second off light cycle. This trap design has been shown to collect 86% or more of live fleas released into a carpeted room (3.1 × 3.3 m) during 20-hour test periods. The ability of this trap to collect such a high percentage of newly emerged fleas in a room provides for a relatively accurate determination of flea development and emergence.

A substantial number of fleas did emerge during the first 21 days, indicating that existing immature flea stages were completing their life cycle. However, flea numbers were reduced in every household by Day 28. Trap collections after that day accounted for only 0.70% of the total fleas caught in the households. Therefore, with a minimal number of fleas collected in the traps after Day 28, it appears that the life cycle was substantially interrupted shortly after therapy was initiated.

This field study was conducted without the inclusion of a placebo group, which might have provided a better comparison and evaluation of the efficacy of the two treatment regimens. However, the investigators felt that the large flea infestations encountered in Florida prohibited the use of a placebo group. Withholding treatment was potentially detrimental to the health and welfare of the dogs and cats.

The combination of nitenpyram (Capstar™) and lufenuron (Program®) was effective in eliminating natural flea infestation from pets and premises in Florida homes. Largely, clients who were allowed to administer nitenpyram “as needed” opted to administer the tablets every other day during the first month, regardless of the level of actual flea burdens. Client perceptions of the severity of the flea problem were not always linked to actual flea numbers. However, once flea infestations were dramatically reduced on pets and in the premises, the rate of administration dropped sharply.

The authors thank Hector Perez and Vicki
REFERENCES