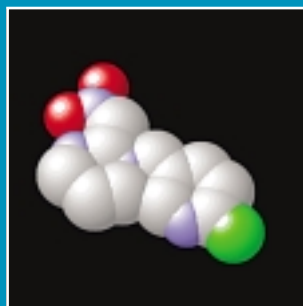


CLINICAL ADVANCES

A SUPPLEMENT TO *COMPENDIUM ON CONTINUING EDUCATION FOR THE PRACTICING VETERINARIAN*®



Clinical Advances, a supplement to *Compendium on Continuing Education for the Practicing Veterinarian*[®], was developed specifically to inform and educate veterinary practitioners and academicians on new products or new uses of existing products in a timely manner. This issue is on advances in the treatment and management of flea infestations in the dog and cat. The material presented is subject to review by experts in the field to ensure accuracy and quality.

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CLINICAL ADVANCES

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A Brief Introduction to Nitenpyram: A New Systemic Flea Adulticide for Cats and Dogs

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 Olivier Tinembart, PhD^a
 Sharron H. Barnett, BS, MS^b
 Scott T. Witte, MS, DVM, PhD, Diplomate, ABT^b

ABSTRACT

Nitenpyram (CapstarTM; Novartis AG, Basel, Switzerland), a neonicotinoid, was developed by Novartis Animal Health to be an oral adulticide against fleas (*Ctenocephalides felis*) on dogs and cats. This article will briefly introduce the structure, physicochemical properties, mode of action, safety and tolerability, pharmacokinetics, dosage and application, and efficacy of nitenpyram.

INTRODUCTION

The most prevalent ectoparasite in dogs and cats is the cat flea (*Ctenocephalides felis*). Over the last few years, several flea control products have been introduced into the veterinary market. Starting in the early 1990s, lufenuron (Program[®]; Novartis AG, Basel, Switzerland), an insect growth regulator/insect development inhibitor (IGR/IDI), was introduced for oral application to dogs and cats. After monthly treatment with lufenuron, the flea life cycle is interrupted and the product thus prevents the buildup of flea populations. In the following years, topically applied insecticides for the treatment of adult fleas were developed and introduced.

Nitenpyram was discovered by Takeda Chemical Industries¹ and developed as a flea adulticide for oral administration to dogs and cats by Novartis Animal Health. See the box at right for the chemical and physical properties of nitenpyram.

MODE OF ACTION

Nitenpyram acts as an agonist to insect-specific

nicotinic acetylcholine receptors in the postsynaptic membranes and does not inhibit acetylcholinesterase.²

SAFETY AND TOLERABILITY

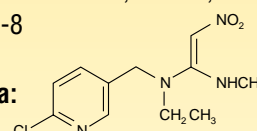
Nitenpyram has a low acute toxicity in the rat (Table 1). It is not an irritant to skin and eyes and is not a dermal sensitizer. Nitenpyram is not mutagenic or teratogenic.

Target animal safety studies in dogs and cats showed that nitenpyram is well tolerated for daily oral administration in puppies and kittens and mature dogs and cats, including reproducing animals.^{3,4}

CHEMICAL AND PHYSICAL PROPERTIES OF NITENPYRAM

Code numbers: CGA 246'916, TI-304,
CAS 120738-89-8

Structural formula:



Chemical class: nitroenamines, chloronicotinyis, neonicotinoids

Common name: nitenpyram

Chemical name: (E)-N-(6-chloro-3-pyridylmethyl)-N-ethyl-N'-methyl-2-nitro-vinylidenediamine

Molecular formula: C₁₁H₁₅ClN₄O₂

Molecular weight: 270.72

Appearance: Pale yellow crystalline powder

Melting point: 83°C–84°C

Vapor pressure: 1.1 x 10⁻⁹ Pa (20°C)

Partition coefficient (n-octanol/water):

log P = -0.64 (25°C)

Solubility in water: 840 g/L (20°C, pH: 7.0)

^aNovartis Animal Health Inc., CH-4002 Basel, Switzerland.

^bNovartis Animal Health, Greensboro, NC, USA.

TABLE 1. Acute Mammalian Toxicity of Technical-Grade Nitenpyram

Acute oral LD ₅₀ (rat, male): 1680 mg/kg
Acute oral LD ₅₀ (rat, female): 1575 mg/kg
Acute dermal LD ₅₀ (rat, male/female): >2000 mg/kg
LD ₅₀ = median lethal dose.

No interactions with commercial ectoparasiticides were found. Concomitant administration of nitenpyram and one of several commercial ectoparasiticides including fipronil, imidacloprid, pyrethrins, cythioate, and carbaryl was well tolerated.^{3,4}

Dogs and cats receiving a wide range of veterinary medicinal products, including vaccines, antibiotics, corticosteroids, deworming medications, and heartworm preventives, were treated with nitenpyram in clinical field studies. No adverse reactions occurred because of the combined use of nitenpyram and any of the medicinal products.^{5,6}

DOSAGE AND APPLICATION

Nitenpyram was developed by Novartis Animal Health as an oral flea adulticide for dogs and cats and is marketed under the trademark Capstar™. The minimum recommended dose is 1 mg/kg body weight. Two dosage forms are available. Tablets containing 11.4 mg nitenpyram are indicated for cats and dogs weighing up to 11 kg (24.2 lb). Tablets containing 57.0 mg are indicated for dogs weighing between 11 and 57 kg (24.2 and 125.4 lb). Puppies and kittens older than 4 weeks and weighing ≥1 kg (≥2.2 lb) can be treated. Tablets can be administered with or without food, as often as once per day, when fleas are seen on the animal.

PHARMACOKINETICS

Pharmacokinetic parameters are shown in Table 2. After administration, nitenpyram is rapidly absorbed from the gastrointestinal tract to reach efficacious blood levels within minutes. Oral bioavailability of nitenpyram is close to unity, and urinary excretion is the predominant route, leaving less than 3% for the fecal route in dogs and less than 6% in cats.^{7,8}

EFFICACY

The efficacy of nitenpyram was demonstrated in a

TABLE 2. Pharmacokinetic Parameters of Nitenpyram in Dogs and Cats

	Dogs	Cats
T _{max}	1.21 (0.65)* h	0.63 (0.36)* h
C _{max}	4787 (782)* ng/mL	4327 (8656)* ng/mL
MRT	4.1 (0.5)* h	10.2 (1.3)* h
T _{1/2}	2.8 (0.7)* h	7.7 (1.1)* h

*Standard deviations.

T_{max} = time of maximum blood concentration.

C_{max} = maximum blood concentration.

MRT = mean residence time.

T_{1/2} = elimination half-life time.

variety of laboratory and field studies. In cats and dogs caged individually, fleas began falling off within 30 minutes after treatment with nitenpyram.⁹

Clinical field studies confirmed the safety and efficacy of nitenpyram (Capstar™) for the treatment of flea infestations on cats and dogs. In a study carried out in eleven veterinary clinics located throughout the U.S., efficacy after treatment with nitenpyram reached 98.6% in dogs and 98.4% in cats within 6 hours.⁵ A similar study in nine veterinary clinics in the United Kingdom resulted in 96.7% efficacy in dogs and 95.2% efficacy in cats.⁶ Both studies also showed that over 80% of the fleas were found off the animals (i.e., fleas were effectively removed and killed with nitenpyram).

Nitenpyram also has been safely used in combination with lufenuron. Studies have shown that no adverse effects were seen in treated animals.^{10–12}

CONCLUSION

Nitenpyram (Capstar™) rapidly and effectively kills fleas on dogs and cats. Studies have shown that it can be used safely in conjunction with insect development inhibitors such as lufenuron. Nitenpyram is very well tolerated by dogs, puppies, cats, and kittens.

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Laboratory Safety Studies of Nitenpyram Tablets for the Rapid Removal of Fleas on Cats and Dogs

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Louis G. Luempert, BS, MS, PhD^a

ABSTRACT

Nitenpyram tablets (Capstar[™]; Novartis Animal Health U.S., Inc.) were evaluated for safety as a treatment for the rapid removal of fleas in cats and dogs 4 weeks of age and older and 2 pounds of body weight or greater.

Five studies were performed with both cats and dogs (a total of ten studies). The studies of cats and dogs, which were of highly similar design, included an acute oral safety study; a 6-week oral safety study beginning at 4 weeks of age; a 6-month oral safety study; a laboratory reproduction study; and a study of potential interactions between nitenpyram and commercial ectoparasiticides. A laboratory study of cats for possible ocular effects was performed in addition to the ten studies.

In the randomized laboratory studies of cats and dogs, nitenpyram with and without concomitant use of lufenuron was evaluated against sham-dosed (touched on the back of the tongue with the handle of a forceps to simulate dosing, but no tablets were given) controls and no controls for treatment periods ranging from 14 days to 9 months and at varying doses, depending on the study. A laboratory study of cats for possible ocular effects after 6 months of oral administration was performed in addition to the ten studies. The series of laboratory studies indicate that nitenpyram is very well tolerated in cats and dogs.

The 202 cats and kittens and 180 dogs and puppies in the studies ranged from 4 weeks old to sexually mature cats and dogs. The current data demonstrate that nitenpyram provides safe removal of fleas in kittens and cats and puppies and dogs.

^aNovartis Animal Health, Greensboro, NC, USA.

INTRODUCTION

Removing the flea burden from cats and dogs quickly is very important to pet owners. Flea infestations may cause flea allergy dermatitis (FAD or fleabite hypersensitivity).¹ Clinical signs of FAD include alopecia, hyperpigmentation, itching, miliary or maculopapular dermatitis, and thickening of the skin. The cat or dog also may develop an odor related to secondary infections with *Staphylococcus intermedius* and *Malassezia pachydermatis*. Fleas act as vectors for a variety of diseases and are carriers of tapeworms. Flea reproduction occurs in an animal's resting areas and bedding and in the environment.

In killing fleas, many pet owners have had problems in the proper application of insecticide sprays, shampoos, and dips to cats and dogs. The development of spot-on flea adulticide formulations has facilitated proper application, and pet owners and veterinarians increasingly have relied on these spot-on topical flea adulticides to control fleas on the pet. However, despite the fact that the safety record of most of these compounds is excellent, changing societal attitudes towards flea adulticide has led to compliance problems and use of questionable alternative therapies such as ultrasonic flea collars, brewer's yeast, and elemental sulfur.

An alternative to topical application of flea adulticide is oral administration. Nitenpyram, a neonicotinoid, is a new systemically active, orally administered flea adulticide that is indicated for the treatment of flea infestations on dogs, puppies, cats, and kittens 4 weeks of age and older and 2 pounds of body weight or greater.

When administered orally, nitenpyram is rapidly

absorbed and eliminated in dogs and cats. Maximum blood levels are reached within 1.2 hours and 0.6 hours in fasting dogs and cats, respectively. The half-life of the drug in dogs and cats is 2.8 hours and 7.7 hours, respectively. When nitenpyram was administered orally to flea-infested dogs and cats, the compound began killing fleas within 30 minutes and achieved >90% effectiveness against adult fleas on dogs within 4 hours and on cats within 6 hours (see Determination of Flea Kill Rate in FOI² or CapstarTM label).

Nitenpyram, which eliminates existing flea burdens and the associated clinical signs, has been safely used with lufenuron. Lufenuron is a highly effective insect development inhibitor (IDI) which prevents eggs and larva from developing into adult fleas. However, the laboratory target animal safety studies described herein were primarily conducted to evaluate the safety of nitenpyram alone and when used with lufenuron.

STUDY SUMMARIES

Introduction

The cat and dog studies described below were performed at independent research laboratories in the United States by professional investigators, including Brian E. Johnson, PhD (Liberty Research; Waverly, NY); Irma M. Grossi, PhD (Liberty Research; Waverly, NY); Edwin I. Goldenthal, PhD (MPI Research; Mattawan, MI); and James Schardein (WIL Research Laboratories; Ashland, OH). In each study described below, bodyweight, hematologic, biochemical, and urologic evaluations were conducted, and animals were observed at least twice daily for signs of overt toxicity.

The study test articles of nitenpyram were supplied as round, beef-flavored tablets and identified as “nitenpyram 11.4 mg” and “nitenpyram 57 mg.” Nitenpyram 11.4 mg was administered to dogs and cats 2 to 25 lb, and nitenpyram 57 mg was administered to dogs 25.1 to 125 lb. All doses of the test article in each study were given on a daily basis.

Acute Oral Safety (Tolerability) Study with Nitenpyram and in Combination with Lufenuron

Purpose: These studies examined the oral safety of nitenpyram at a use rate of ten tablets and when concomitantly dosed with lufenuron at labeled use level in cats and dogs.

Animals: The cat study included 18 domestic shorthair cats (9 male, 9 female) that were 7 to 8 months of age. The dog study included 18 beagle dogs (9 male and 9 female), 7 months of age. In each study, cats and dogs were assigned to one of three treatment groups:

Group	Treatment
1	Control (no treatment)
2	Nitenpyram (ten 11.4-mg tablets or ten 57-mg tablets) + Lufenuron (once according to label)
3	Nitenpyram (ten 11.4-mg tablets or ten 57-mg tablets)

Methods: Controls were sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given). The duration of the studies was 14 days. In dogs, nitenpyram was administered as either ten 11.4-mg tablets per animal once for animals weighing ≤25 lb or ten 57-mg tablets per animal once for animals weighing >25 lb. In cats, nitenpyram was administered as ten 11.4-mg tablets once daily for the duration of the study. Lufenuron was given once according to the label instructions before the initiation of dosing with nitenpyram.

Results: All cats and dogs were in good general health and survived to termination of the studies. No test article-related adverse effects were reported in either study.

Conclusions: Administration of nitenpyram tablets at ten times the recommended dose, with and without lufenuron, did not produce any adverse effects in 7- to 8-month-old cats and 7-month-old dogs.

Six-Week Oral Safety Study Beginning at 4 Weeks of Age with Nitenpyram

Purpose: These studies evaluated the potential cumulative toxicity of nitenpyram tablets administered daily to kittens and puppies, beginning at 4 weeks of age.

Animals: The kitten study included 36 kittens (18 male and 18 female) that were approximately 4 weeks old. The puppy study included 36 beagle puppies (18 male and 18 female), approximately 4 weeks old.

Methods: In each study, kittens and puppies were

assigned to one of three treatment groups: control; nitenpyram oral dosing at labeled use level (one 11.4-mg tablet once daily); and nitenpyram oral dosing at three times the use rate (three 11.4-mg tablets once daily). In both studies, kittens and puppies remained with their dam throughout the study, regardless of their treatment group. Controls were sham dosed. In addition to the standard tests previously described, ophthalmologic tests also were performed.

Results: All puppies survived to termination of the study, except for one in the one-tablet group that was euthanized *in extremis* on day 32 because of coccidiosis. No test article-related changes were reported in any of the variables monitored during the study.

Conclusions: Administration of nitenpyram at one and three times the recommended daily dose for 6 weeks did not produce any clinically significant adverse effects and is safe for use in kittens and puppies as young as 4 weeks.

Six-Month Oral Safety Study with Nitenpyram

Purpose: These studies evaluated the potential cumulative toxicity and dose-response relationship of nitenpyram tablets as high as five tablets administered daily in cats and dogs for 6 months.

Animals: The cat study included 48 domestic shorthair cats (24 male and 24 female) that were 8 weeks old. The dog study included 48 beagle dogs (24 male and 24 female) that were 8 weeks old.

Methods: Animals were assigned to one of four treatment groups: control; nitenpyram oral dosing at labeled use level (one 11.4-mg tablet once daily for animals ≤ 25 lb or one 57-mg tablet once daily for animals > 25 lb); nitenpyram oral dosing at three times the use rate (three 11.4-mg tablets once daily for animals ≤ 25 lb or three 57-mg tablets once daily for animals > 25 lb); and nitenpyram oral dosing at five times the use rate (five 11.4-mg tablets once daily for animals ≤ 25 lb or five 57-mg tablets once daily for animals > 25 lb). Controls were sham dosed. In both studies, animals received ophthalmologic examinations.

Results: In the cat study, animals in all groups, including controls, experienced signs of upper respiratory disease (sneezing, nasal discharge and lacrimation) during the study. Two cats treated with nitenpyram were euthanized: one from the one-tablet group on

study day 28 that had these upper respiratory signs plus dehydration and emaciation and one from the five-tablet group on study day 15 that had nasal discharge, drooling, "seizure-like" spasm, vocalization, and an unsteady gait. These animals were presumed to have a viral infection (based on clinical signs and necropsy findings) complicated by a secondary bacterial infection. All animals in the study had been placed on prophylactic antibiotics before dosing for a facility outbreak of hemolytic *Streptococcus*. The number of Heinz bodies in the red blood cells was increased in the groups treated with nitenpyram compared with controls; however, all values were within normal limits and the increases were not associated with any other abnormalities or clinical signs.

In the dog study, all dogs were in good general health and survived to termination of the study.

Conclusions: The administration of nitenpyram at one, two, and five times the recommended daily dose for 6 months did not produce any clinically significant adverse effects and is safe for use in kittens and puppies as young as 8 weeks.

Laboratory Reproduction Study with Nitenpyram

Purpose: These studies evaluated the reproductive safety of nitenpyram in male and female breeding cats and dogs at one and three times the recommended use rate.

Animals: The cat study included 72 adult cats (18 male and 54 female) that were sexually mature and proven breeders. The dog study included 60 beagle dogs (30 male and 30 female) that were older than 2 years.

Methods: In separate 9-month studies, sexually mature, breeding cats and dogs were assigned to one of three treatment groups: control; nitenpyram oral dosing at labeled use level (one 11.4-mg tablet once daily for animals ≤ 25 lb or one 57-mg tablet once daily for animals > 25 lb); and nitenpyram oral dosing at three times the use rate (three 11.4-mg tablets once daily for animals ≤ 25 lb or three 57-mg tablets once daily for animals > 25 lb). Controls were sham dosed.

In the cat study, reproductive performance was measured using indices to compare the control and treated cats for fertility, birth viability, viability (F_1 survival) and weaning. In the dog study, the control and treatment groups were compared for gonadal function, estrus cycles, mating behavior, conception,

length of gestation, parturition, lactation, the growth and development of offspring, and weaning.

Results: All adult study cats, with the exception of one queen, survived to the termination of the study. The queen was in the one-tablet treatment group. A necropsy report indicates that she suffocated after aspirating a piece of processed paper kitty litter. No clinical signs indicative of toxicity were observed. Body weights, feed consumption, reproductive indices, and spermatogenic variables were unaffected by test article administration.

Axial anterior cortical cataracts were detected in one male in the control group and two of the queens in the three-tablet treatment group. The cataract in the control male was in the right eye. The cataracts were bilateral in the queens from the three-tablet group. The ophthalmologist who examined the cats concluded that the cataracts “may represent normal biologic variation, an age-related change, or could possibly be a treatment effect.” The kittens born were unaffected by test article administration. No ocular changes were seen.

All dogs survived to study termination and no clinical signs indicative of toxicity were observed. Puppies also were unaffected by test article administration. Cleft palate was reported in one puppy from the one-tablet group and two puppies from the three-tablet group. Based on the bloodlines of the puppies and the incidence of cleft palate in the breeding colony, these malformations were not considered to be treatment related.

Conclusions: Because there were no pretreatment ocular examinations, no definitive conclusion could be drawn about the origin of the cataracts in the cats. Oral administration of nitenpyram tablets at one and three times the recommended use rate did not produce any other signs of parental or neonatal toxicity in cats or dogs.

Evaluation of Possible Ocular Effects after 6 Months of Oral Administration of Nitenpyram

Purpose: These studies evaluated cats for possible ocular effects after 6 months of oral administration of nitenpyram tablets. This study was conducted because of results obtained from the laboratory reproduction study with nitenpyram.

Animals: The study included 16 female domestic shorthair cats that were 7 to 8 months of age (only females were included because the cataracts seen at three

times the recommended dose in the laboratory reproduction study already discussed were in female cats).

Methods: Animals were assigned to either sham-dosed control or nitenpyram oral dosing at five times the use rate (five 11.4-mg tablets once daily for animals ≤ 25 lb or five 57-mg tablets once daily for animals > 25 lb). The cats were observed twice daily throughout the study. Clinical examinations were performed weekly. Body weights and food consumption were recorded weekly. Ophthalmic examinations were performed pretest and at 3 and 6 months. Complete physical examinations were performed pretest and at 6 months.

Results: All cats were in good general health and survived to termination of the study. No test article-related changes were seen in the clinical signs, body weights, food consumption, physical, and macroscopic pathology. No test article-related ophthalmologic findings were found.

Conclusions: Administration of five times the recommended dose of nitenpyram tablets daily for 6 months did not produce any evidence of ocular changes.

Study of Potential for Interactions Between Nitenpyram (Five Tablets) and Commercial Ectoparasiticides

Purpose: These studies examined the possibility of adverse interactions between nitenpyram tablets and commercially available ectoparasiticides when used concurrently in kittens and puppies.

Animals: In the kitten study, there were 12 domestic shorthair kittens, 6 to 16 weeks of age. In the puppy study there were 18 beagle puppies (11 males and 7 females), 6 to 16 weeks of age.

Methods: In a study without controls, kittens received nitenpyram (five 11.4-mg tablets once daily) and were assigned to one of four topical treatment groups (Table 1).

In a study without controls, puppies received nitenpyram (five 11.4-mg tablets) and were assigned to one of six treatment groups (Table 2).

Results: All kittens were in good general health and survived to termination of the study, except for one cat in the pyrethrin group. This animal became anorexic and dehydrated during the second study week. The clinical signs and post-study macroscopic and histopathologic evaluations suggested the animal experienced “fading kitten syndrome.”

TABLE 1. Treatment Groups for Cat Drug Interaction Study

Active	Treatment
Carbaryl powder	One application per week; kittens ≥ 6 weeks of age ^a
Fipronil spray	One application; kittens ≥ 8 weeks of age ^a
Imidacloprid spot-on	One application; kittens ≥ 16 weeks of age ^a
Pyrethrin spray ^b	One application per week; kittens ≥ 6 weeks of age ^a

^aAll kittens concurrently received five 11.4-mg nitenpyram tablets once daily for 14 days.
^bActives: Pyrethrins + piperonyl butoxide and n-octylbicycloheptene dicarboximide.

None of the puppies in any of the groups experienced any adverse side effects as a result of the treatments.

Conclusions: Concomitant dosing with nitenpyram (five times the recommended dose) and one of several commercial ectoparasiticides (one times labeled dose) did not produce adverse effects in kittens or puppies.

DISCUSSION

Flea infestation is a widespread problem in cats and dogs that often can result in FAD—a common pet allergy and a well-known source of discomfort for pets. The safe, rapid removal of fleas without adverse events is highly desirable. The objective of the laboratory studies described here was to assess the safety of nitenpyram and, in one study, the safety of nitenpyram when used with the lufenuron, an insect development inhibitor. Nitenpyram also was studied in combination with a number of common commercial ectoparasiticides. The wide-ranging scope of these studies was intended to provide professionals with extensive data on nitenpyram to evaluate the safety of this highly effective flea adulticide.

In six separate laboratory studies of cats and kittens and five studies of dogs and puppies treated with nitenpyram, the treatment was safe and re-

TABLE 2. Treatment Groups for Dog Drug Interaction Study

Active	Treatment
Carbaryl powder	One application per week; puppies ≥ 6 weeks of age ^a
Cythioate tablets	Every three days; puppies ≥ 12 weeks of age ^a
Fipronil spray	One application; puppies ≥ 8 weeks of age ^a fipronil
Spot-on	One application; puppies ≥ 10 weeks of age ^a
Imidacloprid spot-on	One application; puppies ≥ 16 weeks of age ^a
Pyrethrin spray ^b	One application per week; puppies ≥ 6 weeks of age ^a

^aAll puppies concurrently received five 11.4-mg nitenpyram tablets once daily for 14 days.
^bActives: Pyrethrins, piperonyl butoxide and n-octylbicycloheptene dicarboximide.

vealed no adverse effects or toxicities—even at high daily doses, in young animals, and in all stages of reproduction. In the laboratory reproduction study of cats, the presence of cataracts could not be definitively attributed to nitenpyram because no pretreatment ocular examinations were performed. An additional study specifically designed to evaluate ocular effects concluded that no cataracts or other ocular changes occurred even at high doses.

CONCLUSION

Findings obtained in these studies indicate that nitenpyram (CapstarTM), a treatment for flea infestation, is safe and well tolerated in dogs, puppies, cats, and kittens.

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Efficacy of Nitenpyram Against Fleas on Dogs and Cats in a Clinical Field Study

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Sharron H. Barnett, BS, MS^b

ABSTRACT

A clinical field trial was conducted in dogs and cats to demonstrate the efficacy and safety of nitenpyram (Capstar[™]; Novartis AG, Basel, Switzerland) under practical use conditions. A total of 294 dogs and 296 cats infested with fleas were included in the study. Efficacy was determined within 6 hours after administration in three groups: one treated with nitenpyram at the intended dose level of ≥ 1 mg/kg; one treated with nitenpyram plus oral lufenuron; and a placebo group. All animals were evaluated twice within an interval of 7 to 14 days. The nitenpyram plus lufenuron treatment was included to evaluate tolerability of the combination. The nitenpyram-treated groups were combined for statistical analysis. The administration of nitenpyram was very effective in killing and removing fleas from dogs and cats within 6 hours of treatment. The overall efficacy was 96.2% in dogs and 94.1% in cats. The product was well tolerated with no test article-related adverse events observed in any animals that received either nitenpyram alone or the combination of nitenpyram and lufenuron. This study demonstrates that nitenpyram administered at the recommended minimum dose rate of 1 mg/kg bodyweight rapidly and effectively kills fleas under practical use conditions and is well tolerated by dogs and cats with or without the concurrent use of lufenuron.

INTRODUCTION

On-animal flea control presently relies, to a large extent, on compounds having residual activity usually lasting 1 month. The use of an insect growth reg-

ulator/insect development inhibitor (IGR/IDI), such as systemic lufenuron, controls flea populations by interrupting the flea's life cycle, unlike topical insecticides, such as imidacloprid (Advantage[®]; Bayer) and fipronil (Frontline[®] Top Spot[™]; Merial), which kill adult fleas. Interrupting the flea's life cycle is ideal for preventing the build-up of a flea population.¹

Less attention has been given to the development of fast-acting, orally administered compounds that can be used in a variety of flea control situations. This includes the use of adulticides together with IGR/IDIs to kill adult fleas during the pupal window period or adults acquired from the environment. Nitenpyram was identified as a fast-acting compound, and the rapid onset of adulticidal activity of nitenpyram was shown in several laboratory studies.²

This multi-centered well-controlled clinical trial was designed to evaluate the test article's efficacy and safety in the rapid removal of fleas from dogs and cats. The specific objectives were to confirm, under actual field conditions, the dose of nitenpyram for the rapid removal of fleas, the tolerability of its use with lufenuron, and to expand the safety evaluation to include a variety of breeds and ages of dogs and cats under varying clinical conditions.

MATERIALS AND METHODS

The study was conducted in the United States by veterinary investigators at 11 privately owned clinics in eight states. Nitenpyram was supplied by Novartis Animal Health US, Inc. Two tablet sizes were used; the smaller tablet contained 11.4 mg nitenpyram for cats and dogs weighing 1 to 11 kg (2 to 25 lb), and the larger tablet contained 57 mg nitenpyram for dogs weighing 11 to 57 kg (>25 to 125 lb).

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^bNovartis Animal Health Inc., Greensboro, NC, USA.

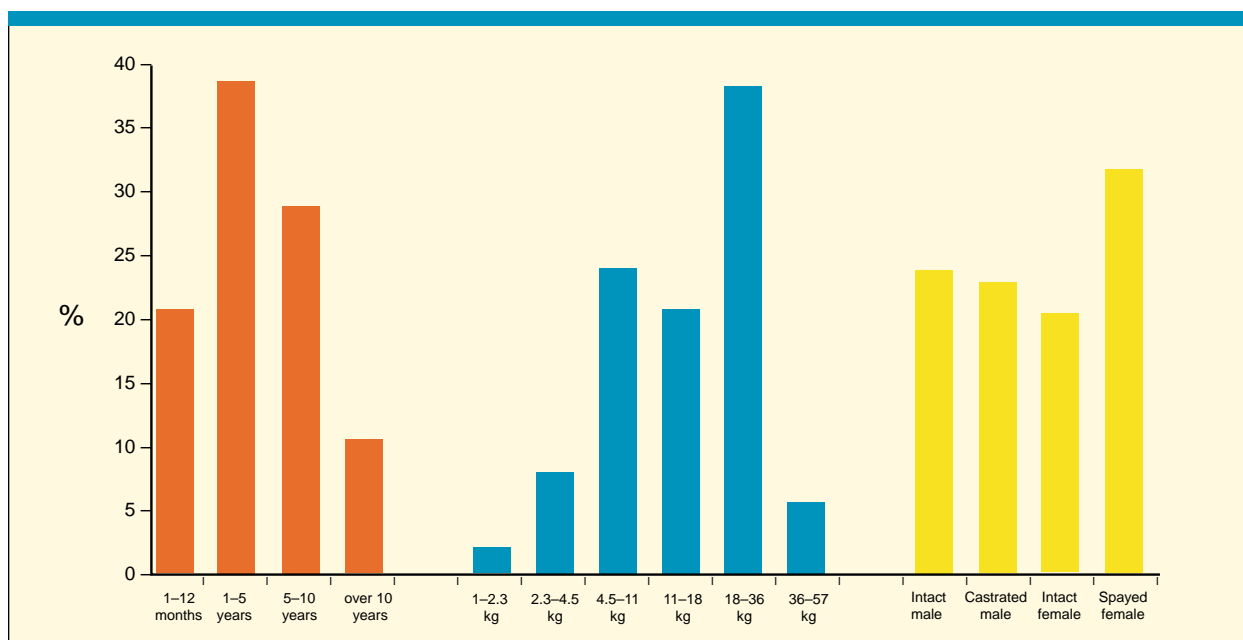


Figure 1. Distribution of the dog study population by age, weight, and sex.

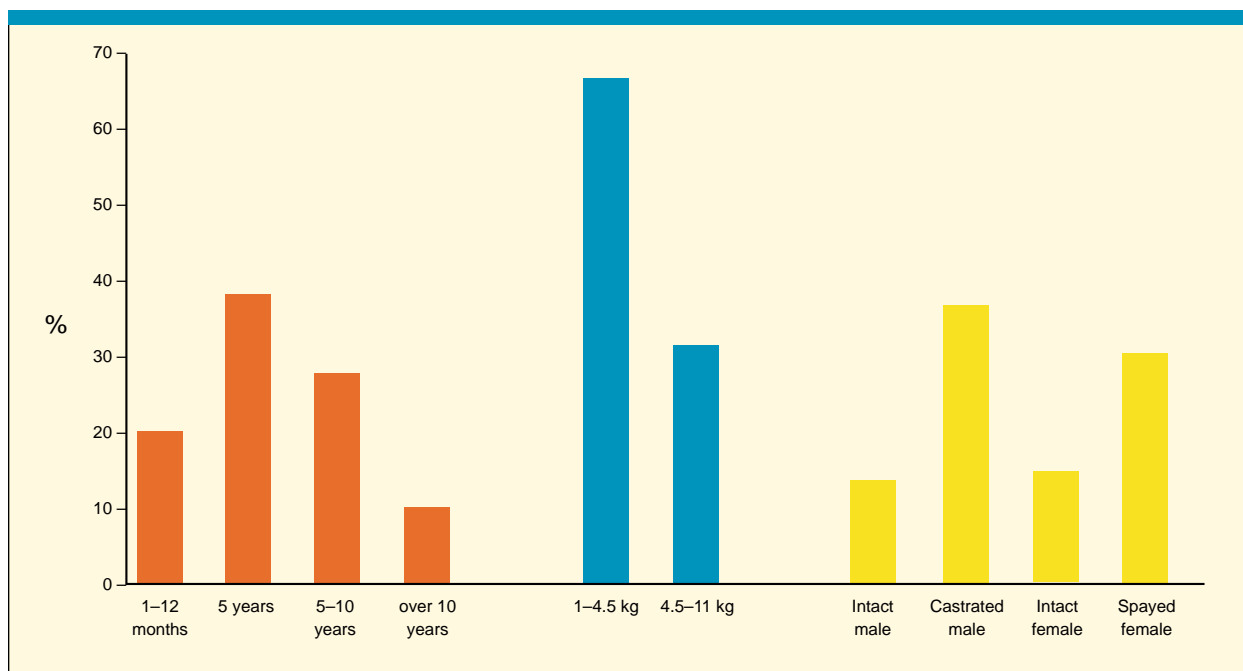


Figure 2. Distribution of the cat study population by age, weight, and sex.

Study Design

Dogs and cats were randomly assigned to one of three treatment groups. Group 1 received nitenpyram alone, group 2 received nitenpyram with concomitant use of lufenuron tablets (dogs) or suspension (cats), and group 3 was the placebo control. The

study was blinded by separation of function, i.e., the persons performing flea counts did not know to which treatment group an animal belonged.

To be eligible for inclusion in the trial, dogs and cats had to be infested with live fleas as determined by spreading the fur between the thumbs. In addition,

TABLE 1. Efficacy as a Percentage of Mortality (Dead and Moribund) of Fleas on Dogs and Cats

Treatment Group	Visit 1		Visit 2 (7 to 14 days later)	
	Dogs	Cats	Dogs	Cats
1 (Nitenpyram)	96.2%	94.1%	95.7%	97.5%
2 (Nitenpyram plus lufenuron)	95.4%	94.2%	96.1%	97.3%
3 (Placebo)	12.3%	13.3%	19.8%	9.9%

the animals had to weigh ≥ 1 kg (2 lb) and be 4 weeks of age or older. Animals in group 1 could not be on lufenuron. However, animals previously administered lufenuron could be enrolled in group 1 if the last lufenuron treatment was given more than 6 months before enrollment. Animals in group 2 had to be treated with lufenuron. They could have been on a treatment schedule when the study began or they could start lufenuron treatment at the start of the study.

At the initial visit all animals received a physical examination, were assigned to a treatment group, and were dosed with their respective treatment by the investigator. After dosing, animals were kept in a cage on a cage rack over a white towel for a holding period of 4 to 6 hours, after which fleas were counted. Fleas found on the towel and by combing the animal were counted.

The owners of animals in treatment groups 1 and 2 received 14 nitenpyram tablets to be given daily until the second visit. At the second visit, 7 to 14 days after the initial visit, the animals again received a physical examination and were dosed, and fleas were counted in a manner similar to that of the initial visit.

Evaluation Criteria

Efficacy was calculated by comparing the number of dead and moribund fleas recovered from the cage and from the animal with the number of live fleas recovered from the cage and from the animal 4 to 6 hours after administration of the test article. Moribund fleas were defined as clearly affected by the treatment but still showing some movement of body appendices. A separate study with nitenpyram showed that fleas classified as moribund were not able to recover and reinfest an animal (unpublished data).

Frequency and severity of undesirable effects were

recorded and evaluated as criteria for establishing tolerability.

RESULTS

Study Population

A total of 294 dogs of 56 breeds and 296 cats of seven breeds were enrolled in the study. Of these animals, 273 dogs and 265 cats completed the study. The distribution of the study population by age, weight, and sex is shown in Figure 1 for dogs and Figure 2 for cats.

Efficacy

The primary endpoint of efficacy was the number and percentage of dead and moribund fleas within 6 hours of dosing. The average number of fleas found on dogs at visit 1 was 109 fleas in the nitenpyram group and 87 fleas in the nitenpyram plus lufenuron group. The highest count on a dog was 829 fleas. On cats the average flea counts in the two treatment groups were 50 and 41 fleas, with the highest count on a cat being 566 fleas. The average flea numbers were drastically reduced by visit 2; dogs had an average of nine fleas in group 1 and 11 fleas in group 2, and cats had an average of two fleas in group 1 and four fleas in group 2.

In dogs, the nitenpyram and the nitenpyram plus lufenuron groups showed an average flea mortality of 96.2% and 95.4%, respectively, within 6 hours of administration at visit 1. The results at visit 2 were similar, with 95.7% mortality in group 1 and 96.1% in group 2 (Table 1).

In cats the nitenpyram and the nitenpyram plus lufenuron groups showed an average flea mortality of 94.1% and 94.2%, respectively, within 6 hours of dosing. The results at visit 2 were similar, with 97.5% mortality in group 1 and 97.3% in group 2 (Table 1).

In contrast, the majority of fleas were found alive

on the dogs and cats in the placebo group (Table 1).

No statistically significant differences were found between the nitenpyram group and the nitenpyram plus lufenuron group in both dogs and cats. Therefore, the two treatment groups were combined for comparison to the placebo group. The result of this analysis indicated a highly significant difference between treatment and placebo groups ($P = .001$). In this study, the overall efficacy of nitenpyram within 4 to 6 hours of administration was 96.1% in dogs and 94.1% in cats.

The majority of fleas in the two treatment groups were recovered dead from the cage, whereas in the placebo group the majority were recovered alive from the animals. For example, at visit 1 only 15.6% of all dead and moribund fleas were recovered from dogs treated with nitenpyram. The remaining 84.4% of the dead and moribund fleas were found in the cage within 6 hours. Similarly, 80% of dead or moribund fleas from dogs treated with nitenpyram plus lufenuron were found in the cage in contrast to the placebo group where 86.1% of the fleas were found alive on the dogs. Similar results were observed in cats.

Tolerability

A normal spectrum of pre-existing conditions was observed before dosing. The test article did not appear to have any negative impact on the pre-existing conditions.

A normal spectrum of clinical manifestations also occurred during the conduct of the study. A total of 111 adverse events were recorded during the study with 75 of these unrelated to the administration of the test article. Causality could not be established between nitenpyram administration and the remaining 36 events.

DISCUSSION

The rapid and effective removal of fleas on dogs and cats achieved with nitenpyram is clearly demonstrated in this clinical field study. The results suggest many potential uses of nitenpyram for a variety of

flea control regimens. With an overall flea mortality of 96.2% in dogs and 94.1% in cats within 4 to 6 hours, nitenpyram provides immediate relief from adult fleas.

The percentage of dead and moribund fleas found in the cage of the nitenpyram groups compared with the percentage of fleas found alive on the placebo animals indicates that dead and moribund fleas are dislodged from the host animal within 6 hours.

No effect of lufenuron on adult fleas was expected because of the short duration of the study. This expectation was confirmed as flea mortality in the nitenpyram group was not statistically different from the nitenpyram plus lufenuron group. However, the study demonstrated that nitenpyram and lufenuron can be used safely in combination.

Nitenpyram is indicated for the treatment of flea infestations. Lufenuron, which was evaluated for tolerability with nitenpyram, is used to control flea populations by interrupting the flea life cycle at the egg and larval stages. When an IGR/IDI and an adulticide are used together, different stages in the life cycle of fleas are affected by different modes of action. This is likely to reduce selection for resistance and thus delay potential development of resistant fleas.³

CONCLUSION

This study demonstrates that nitenpyram (Capstar™; Novartis AG, Basel, Switzerland) administered at the minimum dose rate of 1 mg per kg bodyweight, provides safe, rapid, and effective treatment and removal of fleas from dogs, puppies, cats, and kittens under practical field conditions.

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Efficacy of Nitenpyram Against a Flea Strain with Resistance to Fipronil

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ABSTRACT

A field-collected strain of *Ctenocephalides felis* was suspected to have resistance to fipronil. In vitro bioassays showed a resistance ratio of 26 at the median lethal dose (LD₅₀) level. In vivo efficacy tests with fipronil (Frontline® Top Spot™ and Spray; Merial) were carried out to determine the effect of the measured resistance on product performance and with nitenpyram (Capstar™; Novartis Animal Health U.S., Inc.) to evaluate the efficacy of this new product in the face of resistance.

Six groups of six cats were infested with the resistant strain or with a susceptible strain. Two groups served as control: one for the susceptible strain, one for the resistant strain. One group infested with the susceptible strain was treated with fipronil spot on, and three groups infested with the resistant strain were treated with fipronil spray, fipronil spot on, and nitenpyram, respectively. Treatments were carried out according to label recommendations. Efficacy was measured at days 7, 14, 21, and 28.

Fipronil spot on was fully effective against the susceptible strain. For fipronil spray, efficacy against the resistant strain after 24 hours was 74.6% at day 14, decreasing to 31.8% at day 28. For fipronil spot on, efficacy against the resistant strain after 24 hours was 90.4% at day 14, decreasing to 32.6% at day 28. Eggs collected from surviving fleas were fully viable. Fleas surviving treatment with fipronil at day 30 were put back on the cats. Efficacy of nitenpyram against the resistant strain was 100% after 24 hours.

INTRODUCTION

A number of new flea control products have been made available to veterinarians in recent years. These

products are based on both new chemistry and new application or delivery methods. These products include systemic insect growth regulators/insect development inhibitor (IGR/IDIs) and adulticides such as lufenuron (Program®; Novartis Animal Health U.S., Inc.) and nitenpyram and topically applied insecticides such as fipronil and imidacloprid (Advantage®; Bayer Corp.).

Reduced efficacy of any flea product can be caused by several factors, such as noncompliance with label recommendations, leading to underdosing or loss of product through rub off or wash off in the case of topically applied insecticides.

Although reduced efficacy is an immediate problem for each patient affected, it also increases selection pressure for resistance. Although the overall number of active ingredients used for flea control may remain stable, the concentration on the newer products leads to wider use of fewer compounds and increases selection pressure for resistance.

Information on resistance in fleas is sparse when compared with the vast resistance literature available on insects important in crop protection or public health, though resistance to many compounds has been reported for several flea species including the cat flea *Ctenocephalides felis*.¹ Mechanisms for metabolic resistance and target site insensitivity have been described in fleas.² High variability in insecticide susceptibility between strains and low resistance ratios complicate detection of resistance.³ The effect of differences in susceptibility on product performance needs to be verified in vitro with formulated product.

The first objective of this study was to check whether a field-collected flea strain (from a complaint case) with suspected resistance to fipronil showed physiologic resistance in vitro. The second objective was to evaluate the loss of product perfor-

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mance of fipronil-based products on cats. This was carried out in vivo with measurements of efficacy against adult fleas and viability of eggs from surviving females. In addition, the efficacy of nitenpyram against this resistant flea strain was to be tested to evaluate the usefulness of nitenpyram in resistant fleas.

MATERIALS AND METHODS

Flea Strains

A field-collected strain was compared with the Novartis Animal Health standard susceptible strain in vitro and in vivo.

In Vitro Resistance Ratio

Resistance ratio in vitro was determined by topical application to the lateral thorax of the insects.⁴ After treatment, fleas were transferred to test tubes containing a filter strip. Mortality was determined after a 24-hour holding period. However, the mortality end point was unclear for fipronil. Therefore fleas were held for another 48 hours on artificial feeders to determine final mortality. SAS probit analyses were used to establish a dose/response regression line with 95% confidence limits.

In Vivo Product Performance

For the in vivo product performance test, 36 cats were allocated to six groups of six cats each. The cats were infested with 100 fleas each (50 males and 50 females) on days -1, 7, 14, 21, and 28 of the study. Cats in group 3 were infested on day -1 only.

Groups 1 to 4 were infested with the field-collected strain with resistance to fipronil. The first three groups were treated with fipronil spray (group 1), fipronil spot on (group 2), and nitenpyram (group 3). Group 4 served as an untreated control. Groups 5 and 6 were infested with the susceptible flea strain. Group 5 was treated with fipronil spot on. Group 6 served as an untreated control.

Fleas from cats infested with the resistant strain (groups 1 and 2), which had survived fipronil treatment 48 hours (day 30) after the last infestation, were returned to the cats. The cats were treated with nitenpyram and combed 24 hours later.

The products were applied according to the dose recommended by the manufacturer, which was calculated based on the body weight of each cat on day -1.

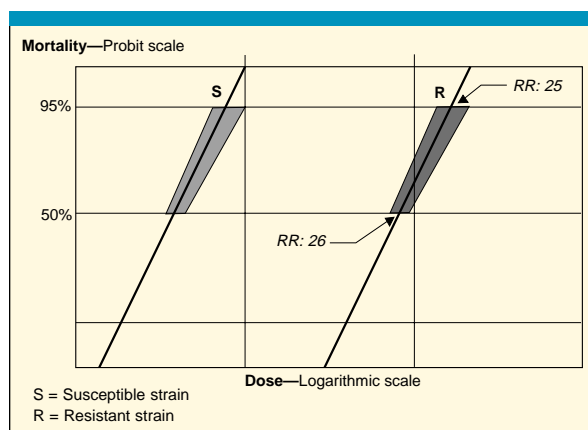


Figure 1. Fipronil dose/effect regression lines with 95% confidence intervals and resistance ratios at the LD₅₀ and LD₉₅ levels.

Flea Counts

The number of live, moribund, and dead fleas was determined by combing each cat with a fine comb for a minimum of 10 minutes. If fleas were seen during the last 2 minutes, combing was continued for another 2 minutes. Flea counts were performed 24 and 48 hours after each infestation. Live fleas recovered after 24 hours were put back on the cats.

Viability of Flea Eggs

Two samples of 50 flea eggs each were collected from fleas with resistance to fipronil from group 1 and group 4 on day 23. The eggs were incubated for 5 to 7 days, and the number of eggs hatched was recorded. The number of cocoons and emerged adults was determined 28 days after egg collection.

RESULTS

Resistance Ratio

The statistically significant differences in susceptibility to fipronil between the susceptible laboratory strain and the field-collected resistant strain are presented in Figure 1. The resistance ratio was 26 at the LD₅₀ level and 25 at the LD₉₅ level. This confirmed the suspected resistance to fipronil in the field-collected flea strain.

Product Performance

An overview of the results is given in Table 1. Fipronil spot on was effective against the susceptible strain on cats. Twenty-four hours after the first flea infestation, efficacy was 91.3%, reaching 100% after

TABLE 1. Efficacy^a of Nitenpyram, Fipronil Spray, and Fipronil Spot On Against a Susceptible and a Resistant Strain of *Ctenocephalides felis*

Group	Flea strain	Treatment	-1 ^b		7 ^b		14 ^b		21 ^b		28 ^b		30 ^c
			24 h ^d	48 h ^d	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	24 h
Group 1	R	Spray	61.5	98.5	94.3	99.1	74.6	83.3	40.2	61.4	31.8	29.7	100
Group 2	R	Spot on	68.5	98.8	93.8	98.1	90.4	95.0	67.3	80.9	32.6	48.0	100
Group 3	R	Nitenpyram	100	100	ND	ND	ND	ND	ND	ND	ND	ND	ND
Group 4	R	Control	14.8	18.3	16.0	22.5	20.0	34.2	0.5	2.0	4.7	19.2	99.8
Group 5	S	Spot on	91.3	100	100	100	100	100	100	100	96.3	100	100
Group 6	S	Control	36.5	38.7	11.3	21.2	22.8	14.3	25.3	27.0	19.3	12.2	100

^aPercentage of flea mortality.

^bDay of infestation (treatment at day 0).

^cNitenpyram treatment of fleas surviving previous treatments at day 30.

^dMortality after treatment at day 0.

R = resistant, S = susceptible, ND = not determined.

48 hours. It remained at 100% until the last infestation at 28 days when efficacy was 96.3% at the 24-hour count and 100% after the 48-hour count.

On cats infested with the resistant strain, efficacy of fipronil spray and fipronil spot on was significantly reduced (Figure 2). With fipronil spot on, mortality at 24 and 48 hours after the initial infestation was 68.5% and 98.8%, respectively. An efficacy of more than 90% was reached 24 and 48 hours after infestations on days 7 and 14. Twenty-four-hour mortality after infestations on days 21 and 28 was

67.3% and 32.6%, respectively. Forty-eight-hour mortality after infestations on days 21 and 28 was 80.9% and 48%, respectively (Figure 2a).

Corresponding mortality values for fipronil spray were 61.5% and 98.5% at 24 and 48 hours after initial infestation. At day 7 efficacy was higher than 90% but dropped to 74.6% and 83.3% at 14 days. At the day 21 evaluation, efficacy was down to 40.2% at 24 hours and 61.4% at 48 hours. It decreased to 31.8% and 29.7% after the infestation on day 28 (Figure 2b).

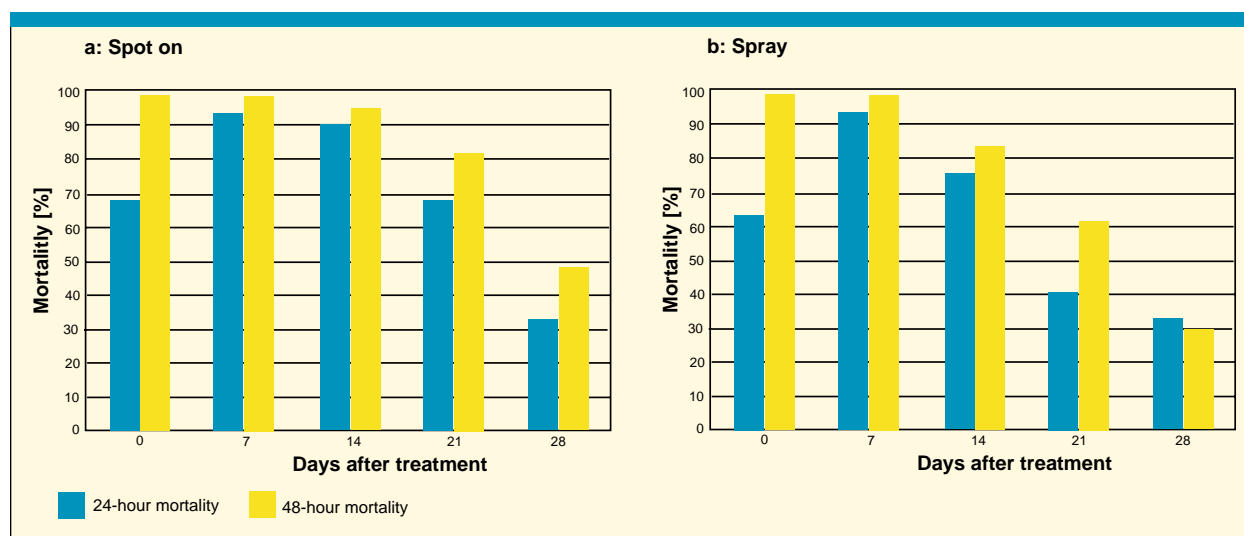


Figure 2. Efficacy of fipronil spot on (a) and fipronil spray (b), applied at the recommended dose rate to cats, against a flea strain with resistance to fipronil.

TABLE 2. Percentage of Eggs Hatched, Cocoons Formed, and Adults Developed

	Group 1 R-Strain Fipronil Spray	Group 4 R-Strain Untreated Control
Eggs hatched	75%	79%
Cocoons formed	74%	78%
Adults developed	68%	74%

Flea Eggs Were Collected 48 Hours After Infestation at Day 21 from Surviving Fleas in Group 1 (Resistant Flea Strain Treated with Fipronil Spray) and Fleas in Group 4 (untreated Control Group of the Same Strain)

Nitenpyram was 100% effective against the fipronil-resistant flea strain 24 and 48 hours after infestation. Nitenpyram was also 100% efficacious against fleas that survived fipronil spray and spot on treatment after the infestation on day 28.

In the control groups, an average of 76.1% of fleas were recovered alive from cats infested with the susceptible flea strain, and an average of 84.8% of fleas were recovered alive from cats infested with the resistant flea strain.

Egg Viability

There was no significant difference in viability of flea eggs collected from the resistant flea strain on cats treated with fipronil spray and from the untreated control group 48 hours after the infestation at day 21 (Table 2). Flea eggs from fleas surviving fipronil treatment were fully viable.

DISCUSSION

Resistance to fipronil was confirmed in vitro in a field-collected flea strain of *Ctenocephalides felis* in the United States. In other insect species, including houseflies,⁵ fruit flies,⁶ and mosquitoes,⁷ cross-resistance between cyclodienes (e.g., dieldrin) and phenyl pyrazole insecticides (e.g., fipronil) has been shown.⁷

A decreased susceptibility in vitro does not necessarily result in product failure. The effect of reduced

susceptibility on product performance has to be tested separately using formulated product at the recommended use concentration in vivo. The resistance ratio of 26 to fipronil at the LD₅₀ level clearly resulted in lower efficacy of the fipronil spray and spot on formulations. In particular, during the second half of the month up to 70% of the fleas survived. This might lead to further selection for fipronil resistance, especially because eggs laid by surviving female fleas were fully viable.

No cross-resistance to nitenpyram was found. Nitenpyram was fully effective against this flea strain. Therefore nitenpyram can be used to treat flea strains with resistance to fipronil.

CONCLUSION

Reduced product performance due to resistance to fipronil spray and spot on was demonstrated after in vitro confirmation of fipronil resistance in a field-collected problem flea strain in the United States. Surviving adult fleas were fully capable of reproduction. Nitenpyram (Capstar™; Novartis Animal Health U.S., Inc.) was 100% effective in treating this flea strain with resistance to fipronil.

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Flea-Related Itching in Cats and Dogs After Treatment with Nitenpyram

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ABSTRACT

The objective of the study was to evaluate itching occasionally observed in cats and dogs shortly after administration of nitenpyram (CapstarTM; Novartis AG, Basel, Switzerland).

Twelve cats and twelve dogs were caged individually, infested with 100 fleas, and dosed with nitenpyram 24 hours later. Cats and dogs were dosed with tablets containing 11.4 mg and 57.0 mg nitenpyram, respectively. Dead fleas began falling off the treated animals within 15 to 30 minutes and were collected in pans placed in the bottom of the animals' cages for 8 hours after administration of nitenpyram. All cats and dogs were observed for signs of itching for 3 hours after treatment. These signs of itching were compared with data obtained when the same cats and dogs were infested with fleas but not treated; or were treated with nitenpyram in the absence of fleas. Number and duration of itching episodes were assessed by videotaping the animals.

The results indicate that the cause of itching was the presence of fleas affected by nitenpyram and that the degree of itching was highly dependent on the individual dog or cat. Treatment with nitenpyram resulted in high numbers of fleas showing increased activity before dying and falling off the host 1 to 2 hours after treatment. During this period, a threefold to sixfold increase in flea-related itching was observed in cats and dogs when compared with untreated flea-infested animals.

INTRODUCTION

Nitenpyram is a neonicotinoid that acts on the insect-specific nicotinic acetylcholine receptors and

has very low mammalian toxicity.¹ Nitenpyram has shown excellent systemic activity against adult fleas after oral administration in controlled in vitro, in vivo, and field studies.^{2,3}

Early in vivo studies involving flea-infested animals treated with nitenpyram showed occasional increased itching shortly after administration of the product. The present study was carried out to determine the cause and development of this itching in cats and dogs.

MATERIALS AND METHODS

Animals and Treatment

Fourteen adult, mixed-breed cats (2.7 to 6.0 kg; seven males and seven females) were allocated to five groups. Groups 1 and 2 comprised three females each, groups 3 and 4 comprised three males each, and group 5 comprised one male and one female as controls. Fourteen adult, mixed-breed dogs (12.3 to 25.0 kg; seven males and seven females) were allocated similarly to five groups.

Animals in each group were subjected to three different treatment regimens, called phases, with each phase separated from the next phase by a nontreatment period of 7 days (Table 1).

Twenty-four hours before treatment each animal was infested with 100 unfed adult *Ctenocephalides felis* from the laboratory colony. Treatment consisted of orally administering one tablet containing 11.4 mg nitenpyram to cats or one tablet containing 57 mg nitenpyram to dogs. Because the rate at which fleas feed varies according to time of day (unpublished data), half of the animals were treated in the morning (8 AM) and half in the evening (4 PM) during phases 1 and 2. Animals were put in individual cages immediately after treatment. Each cage had a false mesh floor 50 mm over the base through which fleas could fall.

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TABLE 1. Treatment Regimens (Phases) of the Experiment

Group	Phase 1 (Day 0) Infested with Fleas ^a	Phase 2 (Day 7) Infested with Fleas ^a	Phase 3 (Day 14) No Fleas Applied ^c
1	Nitenpyram treatment in morning	No treatment (observed in morning)	Nitenpyram treatment
2	Nitenpyram treatment in evening	No treatment (observed in evening)	Nitenpyram treatment
3	No treatment (observed in morning)	Nitenpyram treatment in morning	Nitenpyram treatment
4	No treatment (observed in evening)	Nitenpyram treatment in evening	Nitenpyram treatment
5 (Control) ^b	Nitenpyram treatment in morning	Nitenpyram treatment in evening	No treatment

^a Each animal was infested with 100 unfed adult *Ctenocephalides felis* 24 hours before treatment.

^b Animals in control group were not infested with fleas.

^c Time of day was not considered because there was no flea infestation.

Evaluation of Flea Infestation

At 0.5, 1, 2, 3, and 8 hours after treatment the fleas that had fallen off an animal were collected and counted. After 8 hours each animal was combed with a flea comb and the collected fleas were counted. Untreated animals were treated with a nitenpyram tablet to kill any fleas that remained after combing, and the fallen fleas also were collected and counted.

For each treatment regimen and observation period, percentage of control was calculated according to the formula $100 \times Np/Nt$, where Np is the number of fleas collected during each observation period for

all animals within a treatment and Nt is the total number of fleas collected from all animals within a treatment during the whole phase.

Evaluation of Animal Behavior

Each animal was videotaped during the first 3 hours after treatment. The number of itching episodes and the duration of each episode were recorded at 0.5, 1, 2, and 3 hours after treatment. An episode of itching was defined as the animal touching a part of its body with its mouth or paw in a manner that was more aggressive than grooming. The assessment was subjective but consistent

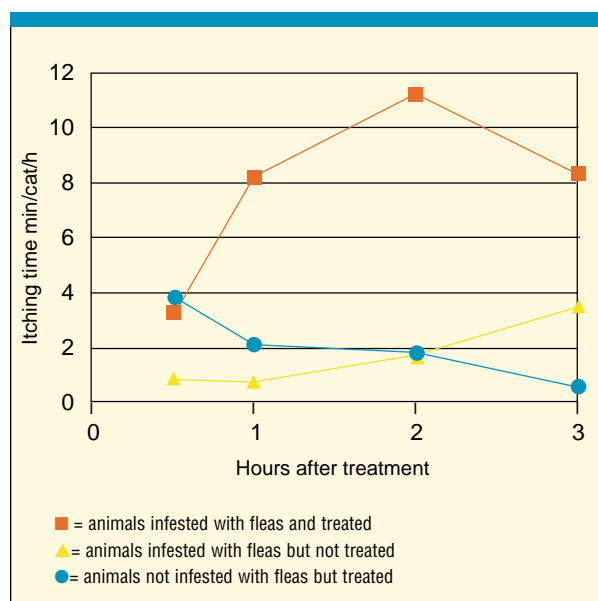


Figure 1. Mean duration of itching in cats (in minutes/hour/cat) during the 3-hour observation after treatment.

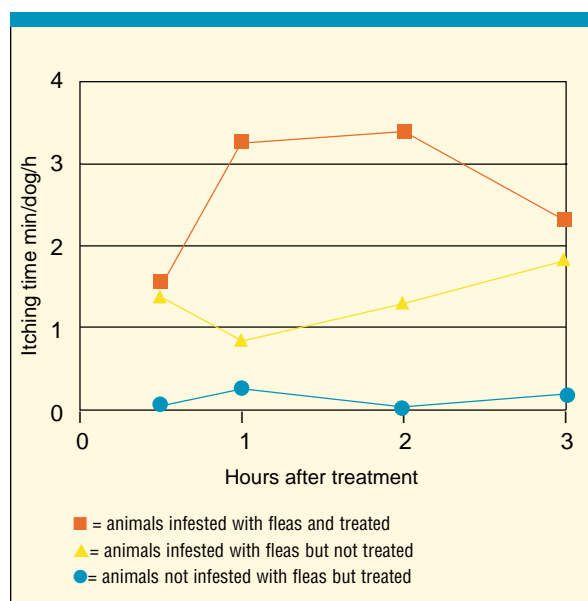


Figure 2. Mean duration of itching in dogs (in minutes/hour/dog) during the 3-hour observation after treatment.

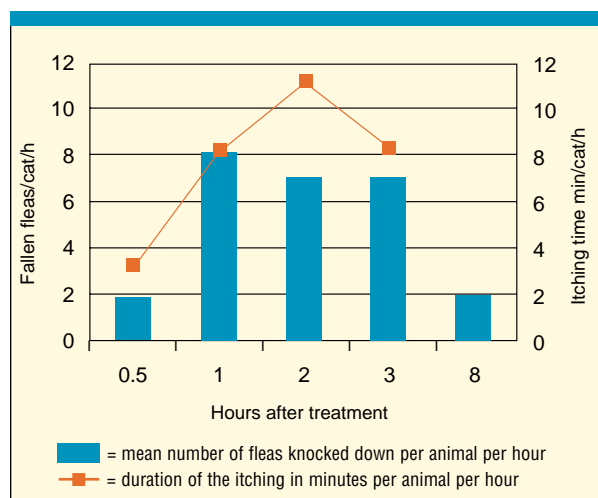


Figure 3. Mean cumulative duration (in minutes) of itching in flea-infested and treated cats during the 3-hour observation after treatment, and mean cumulative number of fleas knocked down up to 8 hours after treatment.

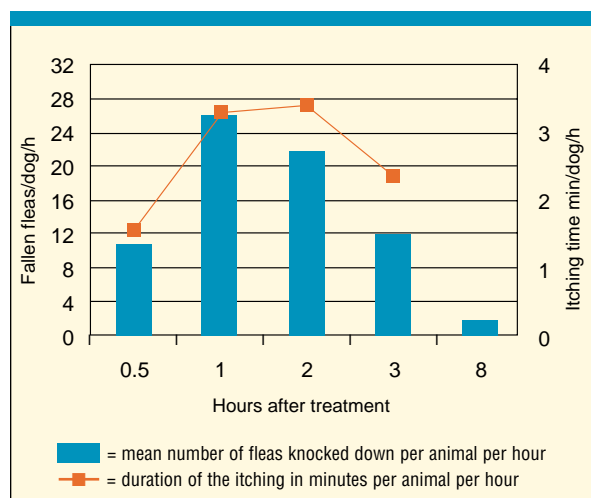


Figure 4. Mean cumulative duration (in minutes) of itching in flea-infested and treated dogs during the 3-hour observation after treatment, and mean cumulative number of fleas knocked down up to 8 hours after treatment.

for all animals and all phases of the study. The mean duration of itching per animal was calculated to the nearest minute for each treatment regimen and observation period.

RESULTS AND DISCUSSION

Flea Knock-Down

Dead fleas started to drop from treated animals within 30 minutes after treatment. Three hours after treatment 64% and 83.6% of fleas had fallen from treated cats and dogs, respectively. Eight hours after treatment the percentage of dead fleas falling from cats and dogs reached 97.7% and 99.1%, respectively, compared with 1.6% and 6.5% from untreated cats and dogs, respectively. No significant difference was observed between males and females or between treatment in the morning and treatment in the evening.

Itching

The study showed that the degree of flea-related itching is variable and dependent on the individual animal.

Durations of itching episodes recorded during the three different phases of the experiment are shown in Figures 1 and 2 for cats and dogs, respectively. Figures 3 and 4 show the correlation between the mean cumulative duration of itching and the mean cumu-

lative number of fleas that fell off the cats and dogs. The data clearly indicate that in treated animals, the primary cause of itching is the flea infestation and is not product related. Treatment with nitenpyram resulted in a high number of fleas falling off the cats and dogs 1 to 2 hours after treatment (Figures 3 and 4). During this time period, a threefold to sixfold increase in flea-related itching was observed in these animals when compared with flea-infested animals left untreated (Figures 1 and 2). The length of itching periods in treated and untreated animals, particularly in dogs, appears to converge toward the end of the observation period, indicating that the effect is transient. No significant difference was observed between male and female animals or between morning and afternoon treatments.

Fleas affected by the neonicotinoid imidacloprid have been observed to stop crawling and to initiate rhythmic trembling of the legs and the body. The effect is due to the blockage of the postsynaptic nicotinic acetylcholine receptor and is irreversible.⁴ The increased trembling of fleas may irritate the host, explaining the observed itching, and may support the correlation of itching to flea density found in this study. The selective toxicity of neonicotinoids to insects has been explained in differences in subunits of the nicotinic acetylcholine receptors.¹ This further supports the finding that itching after administra-

tion of nitenpyram is not a direct effect of nitenpyram on the host animal but rather a result of movements of affected fleas.

CONCLUSION

Occasional itching of flea-infested animals after treatment with nitenpyram (CapstarTM) is not related to the product but is a result of the effects of nitenpyram on the flea and is dependent on the degree of flea infestation. The duration of itching is strongly individual but its timely development correlates closely with the number of fleas knocked down immediately after treatment.

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Speed of Flea Kill with Nitenpyram Tablets Compared to Imidacloprid Spot on and Fipronil Spot on in Dogs

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ABSTRACT

Commercial flea products imidacloprid, fipronil, and nitenpyram were tested to determine the comparative speed of flea kill against existing adult flea infestations. Thirty-six dogs were randomly divided into four groups and infested with 100 unfed adult fleas on Day -2. On Day 0 each of three groups of nine dogs were treated with imidacloprid, fipronil, or nitenpyram according to manufacturer specifications. Nine dogs remained untreated as controls. At 4, 12, and 24 hours following treatment, live flea counts were conducted on three dogs from each group. All products provided significant flea kill with imidacloprid, fipronil, and nitenpyram providing 78.39%, 36.86%, and 100% elimination, respectively, within 4 hours of treatment.

INTRODUCTION

Over the past several years pet owners and veterinarians have successfully relied on spot on topical residual insecticides to eliminate flea infestations on pets. The recent introduction of nitenpyram, a systemically active, orally administered tablet now offers veterinarians and pet owners an additional option for flea treatment. Nitenpyram is rapidly absorbed following oral administration and then rapidly eliminated. Within 1.2 hours and 0.6 hours of administration, peak blood levels are achieved in fasting dogs and cats, respectively. The half-life of the drug in dogs and cats is 2.8 hours and 7.7 hours, respectively.^{1,2}

While residual activity can be an important aspect of a flea product, speed of flea kill can also be a significant issue for veterinarians and pet owners. Rate of flea elimination can be important in providing pets relief from flea infestations and is important for pet owner perception of flea product performance. In a previous study imidacloprid was found to eliminate 88.7% and 100% of fleas on dogs within 8 and 12 hours, respectively.³ In another study, imidacloprid and selamectin eliminated 96.7% and 11.0% of fleas on dogs within 12 hours of treatment, respectively.⁴ While some topical formulations have demonstrated a rapid kill rate, this project was conducted to compare the rate of kill of orally administered nitenpyram tablets (CapstarTM) with imidacloprid spot on (Advantage[®]) and fipronil spot on (Frontline[®] Top SpotTM) against existing flea infestations on dogs.

MATERIALS AND METHODS

Animals and Research Design

Thirty-six adult male shorthaired dogs weighing between 9.8 and 14.6 kg were randomly distributed into four treatment groups of nine dogs each. All dogs were housed in individual stainless steel cages and cared for in accordance with guidelines established by the Institutional Animal Care and Use Committee at Kansas State University (IACUC protocol #1792). Treatment groups were housed in separate rooms within the same building to minimize contamination between groups. No drugs, baths, shampoos, or pesticides were administered to the dogs during the preconditioning phase or the course

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of the study except the commercially available flea treatments specified. Prior to the Day -2 infestations, dogs were verified to be free of fleas by visual inspection for flea feces and adults and by combing.

Dogs in group 1 served as untreated control animals. Group 2 dogs were treated with imidacloprid, 9.1% w/w (weight/weight) spot formulation (Advantage™ Flea Adulticide, Bayer Animal Health). Group 3 dogs were treated with fipronil, 9.7% w/w spot formulation (Frontline® Top Spot™, Merial Animal Health). Group 4 dogs were treated with nitenpyram (Capstar® Tablets, Novartis Animal Health) administered as either an 11.4-mg or a 57-mg tablet depending upon the weight of the individual dog.

Speed of kill was determined by removing fleas from three dogs in each group at 4, 12, and 24 hours post-treatment. Flea removal was conducted by combing each dog thoroughly for 10 minutes by two members of the flea team. The comb used for flea removal was fine toothed, with 12 to 13 teeth per centimeter (Safari Flea Comb, Whitco, Centereach, NY). If five or more fleas were recovered during the initial 10-minute combing period, the dogs were combed for an additional 5 minutes. If any fleas were recovered during this second combing period, the dogs were combed for an additional 5 minutes.

Recovered fleas were considered live if they were actively moving and could move upright in examiner's hand or in a plastic collection bag. Fleas were considered dead if they were inactive or moribund (slight movement of limbs, no progress motion, or inability to stand and move upright).

Procedures

On Day -2, all dogs were infested with 100 fleas, one to three days post-emergence. A laboratory strain of *Ctenocephalides felis*, established and maintained as a closed colony at Kansas State University since 1990 (KS1) was used. On Day 0 dogs in groups 2, 3, and 4 were treated with the appropriate flea adulticide according to manufacturer's label directions. Three dogs from each of the four groups were randomly selected for combing at each of the three time intervals. Treatments were staggered for the dogs in each subgroup at 20-minute intervals (Time 0, 0 + 20 minutes, and 0 + 40 minutes). This was done to allow the combing teams up to 20 minutes for combing each dog, as required by the proto-

col, at exactly 4, 12, and 24 hours following treatment. At each of the three time intervals, fleas were collected from pans beneath the three dogs previously selected from each group and the dogs were combed to remove remaining fleas. Fleas collected by either procedure were counted and their live-dead status was noted.

Statistical Methods

Analysis of variance techniques were used to determine if differences existed between any of the treatment groups. A square root transformation was employed to normalize the count data. All analyses were conducted using the SAS Statistical Analysis System version 8.01 (SAS Institute, Cary, NC).

RESULTS

Dogs were treated with 11.16 mg/kg (std 1.76), 22.15 mg/kg (std 1.84) and 2.88 mg/kg (std 1.74) fipronil, imidacloprid, and nitenpyram, respectively. Flea counts and percentage of flea kill are provided in Table 1. As indicated, dogs in the control group maintained a mean of 78.67, 74, and 59.67 fleas, respectively, at 4, 12, and 24 hours after treatment. A mean of 17 (78.39% kill) live fleas were recovered

TABLE 1. Mean Flea Counts and Percent Kill at 4, 12, and 24 Hours Following Treatment

Treatment	Treatment Period (hours post-treatment)			
	0	4	12	24
Nitenpyram				
Mean Flea Count	100	0	0	0
% Kill		100	100	100
Fipronil				
Mean Flea Count	100	49.67	7.33	0
% Kill		36.86	90.09	100
Imidacloprid				
Mean Flea Count	100	17	0	0
% Kill		78.39	100	100
Control				
Mean Flea Count	100	78.67	74	59.67

TABLE 2. P-values Obtained from Analyses of Variance to Test for Treatment Differences at Every Time Period

Hour	Treatment	Treatment			
		Control	Fipronil	Imidacloprid	Nitenpyram
4	Control		0.0049	<.0001	<.0001
4	Fipronil	0.0049		0.0003	<.0001
4	Imidacloprid	<.0001	0.0003		<.0001
4	Nitenpyram	<.0001	<.0001	<.0001	
12	Control		<.0001	<.0001	<.0001
12	Fipronil	<.0001		<.0001	<.0001
12	Imidacloprid	<.0001	<.0001		1.000
12	Nitenpyram	<.0001	<.0001	1.000	
24	Control		<.0001	<.0001	<.0001
24	Fipronil	<.0001		1.000	1.000
24	Imidacloprid	<.0001	1.000		1.000
24	Nitenpyram	<.0001	1.000	1.000	

from the imidacloprid group and 49.67 (36.39% kill) live fleas were recovered from fipronil treated dogs at 4 hours. No live fleas were recovered from dogs (100% kill) treated with nitenpyram when combed 4 hours after treatment. At the 12-hour combing period imidacloprid and fipronil had provided 100% and 90.09% (7.33 fleas) kill, respectively. All three treatments produced 100% elimination of established flea infestations on dogs at 24 hours post-treatment. Results from the analysis of variance are presented in Table 2.

The results obtained at 4 hours indicate that all treatments provided significant reduction of flea infestations as compared to untreated controls. Imidacloprid provided significantly better control than fipronil, and nitenpyram provided significantly better kill than either fipronil or imidacloprid. Again, at 12 hours, all products showed significant reduction of flea infestation; imidacloprid and nitenpyram were both significantly better than fipronil, but no difference existed between imidacloprid and nitenpyram. At 24 hours, all treatments provided significantly better flea reduction than the control group, but were statistically equivalent relative to each other (Figure 1).

DISCUSSION AND CONCLUSIONS

While all three products provide 100% elimina-

tion of fleas within 24 hours of treatment, the data demonstrate that nitenpyram reduced flea numbers on dogs significantly faster than either fipronil or imidacloprid. The veterinary community is currently using several excellent flea products with prolonged residual activity. While nitenpyram has a short duration of action, the remarkable rapid elimination of fleas provided by this orally administered drug offer several possible clinical uses.

Animals on lufenuron, lufenuron-milbemycin, methoprene, or pyriproxifen in long-term preven-

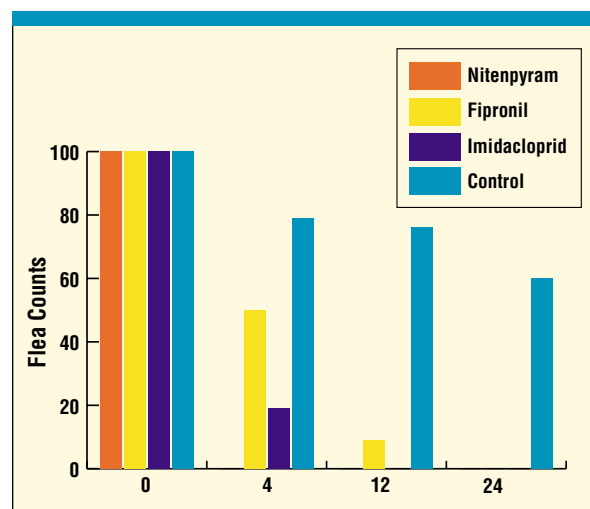


Figure 1. Mean flea count comparison.

tion programs occasionally encounter fleas in the environment (hitchhiker fleas). These fleas are unable to reproduce because of their exposure to insect development inhibitors or juvenile hormone mimetics, but they can still cause pet discomfort, and therefore need to be eliminated. In studies, nitenpyram has been used safely with lufenuron.⁵ Administration of nitenpyram on an “as needed” basis provides rapid elimination of fleas. Nitenpyram can also be used for rapid elimination of pet flea burdens prior to boarding or surgery, prior to release from clinic, and for expeditious treatment of animals at animal shelters.

While compounds such as fipronil, imidacloprid, and selamectin can provide excellent control of established flea infestations, nitenpyram can also be used to help eliminate existing flea infestations.

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