

Effect of topical application of fipronil in cats with flea allergic dermatitis

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Objective—To determine whether topical application of a 10% fipronil solution would control signs of flea allergic dermatitis in cats housed under natural conditions.

Design—Multicenter open clinical trial.

Animals—42 client-owned cats with flea allergic dermatitis.

Procedures—Study cats along with all other cats and dogs living in the same houses were treated with 10% fipronil solution topically on days 0, 30, and 60. Flea counts and clinical assessments were performed on study cats on days 0, 14, 30, 60, and 90.

Results—Percentage reductions in geometric mean flea counts on days 14, 30, 60, and 90, compared with day-0 geometric mean count, were 75, 73, 85, and 94%, respectively. Pruritus score was significantly improved at each examination after day 0, and pruritus was reduced or eliminated in 31 of 40 (78%) cats at the final examination. Similarly, scores for severity of miliary dermatitis and alopecia were significantly improved at each examination, except for alopecia score on day 14. Overall treatment efficacy, assessed on day 90, was excellent for 28 (70%) cats, good for 6 (15%), moderate for 3 (7.5%), and poor for 3 (7.5%).

Conclusions and Clinical Relevance—Results suggest that monthly topical application of fipronil is effective for treatment of flea allergic dermatitis in cats housed under natural conditions. (*J Am Vet Med Assoc* 2002;221:254–257)

Flea allergic dermatitis (FAD) is 1 of the most common skin diseases in cats.¹ The flea most commonly recovered from domestic cats is the cat flea, *Ctenocephalides felis*.^{2,3} Although adult *C felis* are permanent ectoparasites on cats, the immature stages of this parasite are found in the environment.⁴ Therefore, flea control has traditionally involved both topical and environmental use of insecticides.

Fipronil, a synthetic molecule that has potent insecticidal and acaricidal properties, belongs to the

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phenylpyrazole family^{5-7,a} and acts as an antagonist at the γ -aminobutyric acid (GABA) receptor. In insects, the GABA receptor is a neurotransmitter that acts as the major inhibitor in the CNS and at neuromuscular junctions. Fipronil kills adult fleas by binding to a site in the chloride channel of GABA receptors and inhibiting GABA-regulated chloride flux into nerve cells.⁶

The purpose of the study reported here was to determine whether topical application of a 10% fipronil solution would control signs of FAD in cats housed under natural conditions.

Materials and Methods

Study cats—The study was designed as a multicenter trial that included 3 veterinary hospitals in Georgia and 1 veterinary hospital in Florida. Client-owned cats determined to have FAD on the basis of a history of flea infestation and clinical findings consistent with FAD (ie, pruritus, miliary dermatitis [crusted papular lesions], alopecia, and eosinophilic granuloma complex lesions involving the neck, dorsal lumbosacral area, caudomedial aspect of the thigh, or ventral aspect of the abdomen) were eligible for inclusion in the study. Serologic testing for flea antibody titers^b was used to support the diagnosis of FAD. Cats were included in the study only if cytologic examination of skin scrapings did not reveal any mites and fungal culture of skin scrapings and hairs did not yield any growth of dermatophytes.

Treatments—Study cats, along with all other cats and dogs living in the same houses as the study cats, were treated topically with a 10% fipronil solution^c administered according to label directions. All cats were at least 12 weeks old, and all dogs were at least 10 weeks old. All cats and dogs received a single spot application of fipronil between the shoulder blades on day 0 and again on approximately days 30 and 60. No other topical or environmental flea treatments were used during the study.

Flea counts—Flea counts were performed on study cats on days 0, 14, 30, 60, and 90. For each flea count, cats were combed for 10 minutes, and all removed fleas were then counted.

Clinical assessments—Clinical assessments were performed on study cats on days 0, 14, 30, 60, and 90. At each time, scores for severity of pruritus, miliary dermatitis, alopecia, and eosinophilic granuloma complex lesions were assigned. Severity of pruritus was assessed by the owner and scored as 0 (absent), 1 (mild), or 2 (intense). Severity of miliary dermatitis was assessed by the investigator and scored as 0 (absent), 1 (localized), or 2 (generalized). Severity of alopecia was assessed by the investigator and scored as 0 (absent), 1 (localized), or 2 (extensive). Severity of eosinophilic granuloma complex lesions was assessed by the investigator and scored as 0 (no lesions), 1 (single lesion), or 2 (several lesions). On days 14, 30, and 60, an overall assessment of clinical improvement, compared with day 0, was made by the investigator; degree of improvement was scored as 1 (definite improvement), 2 (moderate improvement), 3 (no improvement), or 4 (worsening of the condition). On day 90, the investigator made an overall

assessment of treatment efficacy, with clinical response scored as 1 (excellent), 2 (good), 3 (moderate), or 4 (poor).

Data analysis—Flea counts at each visit were transformed to the natural logarithm ($\ln [\text{count} + 1]$) for calculation of geometric means. Percentage reduction in flea count on days 14, 30, 60, and 90 was calculated as $100 \times (1 - [\text{geometric mean flea count on day 14, 30, 60, or 90} / \text{geometric mean flea count on day 0}])$. Lower 1-sided 95% confidence limits on the percentage reduction in flea count were calculated for days 14, 30, 60, and 90. Least-squares geometric means from a mixed-model analysis were used for these calculations. The analysis was based on a mixed-model analysis for a partially hierarchical design including the factors clinic, animal within clinic, and time (before or after treatment). The interaction of time and clinic was not significant ($P > 0.20$) and was not included in the model.

For analysis of the degree of clinical improvement on days 14, 30, and 60, a sign test was used to compare the proportion of cats that had improved since the initial visit (day 0) with the proportion of cats in which the condition had worsened. This test assumes that without treatment, the probability of the condition improving is equal to the probability of the condition becoming worse. Changes from baseline scores for severity of pruritus, miliary dermatitis, alopecia, and eosinophilic granuloma complex lesions were analyzed with 2-sided Wilcoxon signed-rank tests. For each animal, variable, and time point, the score at the initial visit (day 0) was subtracted from the posttreatment score. For all analyses, values of $P \leq 0.05$ were considered significant.

Results

Study cats—Forty-two cats (28 domestic shorthair cats, 6 domestic longhair cats, 5 domestic medium-hair cats, 1 Persian, 1 Manx, and 1 Chartreux) were enrolled in the study. There were 3 sexually intact females, 24 neutered females, 1 sexually intact male, and 14

neutered males. Cats ranged from 1 to 14.4 years old (mean, 6.6 years) and weighed between 2.4 and 9.1 kg (5.3 and 20 lb; mean, 4.9 kg [10.8 lb]). All cats had a history of flea infestation and pruritus and had lesions involving the skin of the neck, dorsal lumbosacral area, caudomedial aspect of the thigh, or ventral aspect of the abdomen. Thirty-three (79%) cats had fleas or flea feces on them at the time of the initial visit (day 0). Thirty-nine cats had miliary dermatitis, 24 had alopecia, and 4 had eosinophilic granuloma complex lesions. All cats were seropositive for flea antibody antigen; titers ranged from 221 to 4,859 Ab-E/ml (mean, 2,032 Ab-E/ml).

Forty cats completed the study, although 1 of these cats was not evaluated on day 14 but was evaluated on days 30, 60, and 90. One of the 2 cats that did not complete the study was not returned for reevaluation on days 60 and 90; the other was not returned for evaluation on day 90. Because of severe pruritus and lesions that resulted in extreme discomfort, glucocorticoids were administered to 2 cats in which the condition had worsened after the initial treatment. One of these cats was given prednisone, PO, on days 14 through 18; the other was given prednisone, PO, on days 30 through 34. No other study cats received any other treatments for FAD during the study.

Flea counts—At each posttreatment visit, cats had significantly ($P < 0.01$) fewer fleas than they had had at the initial visit (Table 1).

Clinical assessments—All study cats had mild (33 cats; 79%) or intense (9; 21%) pruritus at the initial visit. Pruritus score improved significantly ($P < 0.01$) at each posttreatment visit (Table 2). Pruritus was

Table 1—Reduction of flea burdens in cats with flea allergic dermatitis (FAD) treated topically with 10% fipronil solution on days 0, 14, 30, and 60

Variable	Day 0	Day 14	Day 30	Day 60	Day 90
No. of cats	42	41	42	41	40
Geometric mean flea count	2.99	0.75	0.80	0.45	0.19
Percentage reduction in flea count*	NA	75	73	85	94
Lower 95% confidence limit†	NA	68	66	80	91

*Calculated as $100 \times (1 - [\text{geometric mean flea count on day 14, 30, 60, or 90} / \text{geometric mean flea count on day 0}])$.
†Lower 95% confidence limit of the percentage reduction in flea count.

Table 2—Results of dermatologic examinations of cats with FAD treated topically with 10% fipronil solution on days 0, 14, 30, and 60

Variable	No. of cats				
	Day 0	Day 14	Day 30	Day 60	Day 90
Pruritus score					
0 (absent)	0	15	24	25	29
1 (mild)	33	23	14	11	10
2 (intense)	9	3	4	5	1
Miliary dermatitis score					
0 (absent)	3	17	24	25	26
1 (localized)	29	20	13	13	11
2 (generalized)	10	4	5	3	3
Alopecia score					
0 (absent)	18	24	30	32	33
1 (localized)	22	16	12	8	7
2 (extensive)	2	1	0	1	0
Eosinophilic granuloma complex lesion score					
0 (no lesions)	38	37	39	38	39
1 (single lesion)	1	2	2	1	0
2 (several lesions)	3	2	1	2	1

Table 3—Overall assessment of clinical improvement, compared with pretreatment condition, in cats with FAD treated topically with 10% fipronil solution on days 14, 30, and 60

Clinical condition	No. of cats		
	Day 14	Day 30	Day 60
Definite improvement	15	22	25
Moderate improvement	16	13	8
No improvement	8	6	7
Worse	2	1	1

reduced or eliminated in 31 of 40 (78%) cats at the final visit.

Thirty-nine (93%) cats had miliary dermatitis at the initial visit. Lesion scores improved significantly ($P < 0.01$) at each posttreatment visit (Table 2). On day 90, 26 of 40 (65%) cats were free of miliary dermatitis.

Twenty-four (57%) cats had alopecia at the initial visit. Alopecia scores were significantly ($P < 0.01$) improved on days 30, 60, and 90 but not on day 14 (Table 2). Thirty-three of 40 (83%) cats were free of alopecia on day 90.

Three of the 4 cats that had eosinophilic granuloma complex lesions at the initial visit were free of lesions on day 90 (Table 2).

Percentages of cats with moderate or definite clinical improvement on days 14, 30, and 60 were 76, 83, and 81%, respectively (Table 3). At all 3 times, the proportion of cats that had improved was significantly ($P < 0.01$) higher than the proportion that had become worse. Overall treatment efficacy, assessed on day 90, was excellent for 28 (70%) cats, good for 6 (15%), moderate for 3 (7.5%), and poor for 3 (7.5%).

Discussion

Results of the present study suggest that fipronil is effective for treatment of FAD in cats housed under natural conditions. Flea counts and severity of clinical signs were significantly reduced after topical application of a 10% fipronil solution and were still significantly reduced 30 days after the third of 3 monthly applications. Overall treatment efficacy was judged to be excellent or good in 34 of 40 (85%) cats.

Several previous studies have shown that fipronil is effective in reducing the number of fleas on treated animals. For instance, 2 studies^{d,e} of cats experimentally infested with fleas have documented that a single application of 10% fipronil solution has excellent acute and residual activity against *C felis*. In both studies, there was a reduction in the cats' flea burdens within 24 hours after application of fipronil. Residual efficacy of fipronil, defined as a $\geq 95\%$ reduction in flea burden within 24 hours after application of fleas, was estimated to be 3 to 5 weeks. Similarly, in field trials^{8,c} of cats housed under natural conditions, between 52 and 78% of cats did not have any fleas 5 weeks after a single application of fipronil, and between 43 and 53% of cats did not have any fleas 7 weeks after a single application. In 2 studies^{9,10} of cats kept in simulated home environments, monthly applications of 10% fipronil solution provided 100% control of fleas on cats for the duration of the studies. In a study^f of household cats and dogs infested with fleas that were treated with 5 monthly applications of 10% fipronil solution, 77% of

the cats and 87.5% of the dogs were completely free of fleas at the end of the study. Finally, in a study¹¹ of dogs and cats treated with fipronil 3 times at monthly intervals, flea burdens on the animals were reduced by 96.5%, and flea numbers in the home environment were reduced by 98.6%. In the present study, 33 of the 42 (79%) cats had fleas or flea feces on them at the time of the initial visit, and flea counts were reduced, on average, 94% 30 days after the last administration of fipronil, compared with counts at the time of the initial visit. These findings confirm that fipronil has persistent efficacy against fleas, even under the conditions of the present study in which cats were housed in their home environments.

However, treatment of cats with FAD should be considered successful only if there is resolution of clinical signs in cats housed under natural conditions, along with reduction or elimination of the flea population. Of the 42 cats in the present study, all 42 (100%) had pruritus, 39 (93%) had miliary dermatitis, 24 (57%) had alopecia, and 4 (10%) had eosinophilic granuloma complex lesions at the time of the initial visit. Thirty days after the third monthly application of fipronil, only 11 of 40 (28%) cats had pruritus, only 14 (35%) had miliary dermatitis, and only 7 (17%) had alopecia. Additionally, only 1 of the 4 cats with eosinophilic granuloma complex lesions at the initial visit still had lesions at the end of the study. These results are consistent with data from a field study¹² performed in southern Europe in which flea-infested cats were treated with a single application of 10% fipronil solution. In that study, all cats had fleas, and 63% had pruritus at the initial visit. Five weeks after treatment, 78% of the cats were free from fleas, and 82% were free from pruritus. Although only 23% of the cats had dermatologic lesions at the time of the initial visit, the prevalence of these lesions was reduced to 4% 5 weeks after treatment.

In the present study, overall treatment efficacy was judged to be good or excellent in 34 of 40 (85%) cats. This further supports the suggestion that fipronil is effective for treatment of flea allergic dermatitis in cats, even without concomitant environmental use of adulticides or insect growth regulators. Possible explanations for the moderate or poor treatment efficacy in the remaining 6 cats include continuous outdoor environmental exposure to fleas, concurrent food allergies, and atopy.

^aHeska Corp, Fort Collins, Colo.

^bFrontline Topspot for Cats and Kittens and Frontline Topspot for Dogs and Puppies, Merial Ltd, Duluth, Ga.

^cHunter JS, Keister DM, Jeannin P. Fipronil: a new compound for animal health (abstr), in *Proceedings*. 39th Annu Meet Am Assoc Vet Parasitol 1994;40.

^dPostal JM, Longo J, Hunter JS, et al. Efficacy against fleas (*Ctenocephalides felis*) in cats of two topical formulations of fipronil (FRONTLINE Spray and FRONTLINE Top Spot) under experimental infestation: an overall analysis of various studies (abstr), in *Proceedings*. 4th Int Symp Ectoparasites Pets 1997;81.

^ePostal JM, Le Nain S, Fillon F, et al. Efficacy of a 10% fipronil spot-on formulation against cat flea infestations (*Ctenocephalides felis*) in cats (abstr), in *Proceedings*. Br Small Anim Vet Assoc Congr 1996;31.

^fMeo N, Dryden M, Irwin J, et al. Monitoring of treated dogs and cats

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