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Evaluation of the efficacy and safety of a novel formulation of metaflumizone in cats naturally infested with fleas in Europe

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Abstract

The efficacy and safety of a novel spot-on formulation of metaflumizone (ProMeris[®] for Cats, Fort Dodge Animal Health, Overland Park, KS) was assessed in cats naturally infested with fleas in a multiregional, clinical field study. Sixteen veterinary clinics in Germany and eight clinics in France enrolled patients to the study. A total of 173 cats with flea infestation qualified as primary patients and were randomly allocated to one of the two treatments in a ratio of approximately 2:1 for metaflumizone (minimum dosage of 40 mg/kg) or fipronil (at the recommended label rate). Clinical examinations and baseline parasite counts were performed on Day 0 prior to treatment. Flea counts and safety evaluations were repeated at approximately 2-week intervals for 8 weeks. Both treatments resulted in consistent reductions (>84%) in flea numbers throughout the study, but metaflumizone resulted in numerically higher reductions on most count days. Within groups the flea reduction was highly significant ($p < 0.0001$) compared to baseline at all observation periods. The efficacy of metaflumizone against fleas compared to baseline was 91.0%, 89.4%, 90.8% and 90.7% at Day 14, 28, 42 and 56, respectively. The corresponding efficacies for fipronil were 91.7%, 86.9%, 84.6% and 87.7%. Metaflumizone was highly effective in controlling existing infestations of fleas on cats and was effective against reinfestation for at least 56 days. Metaflumizone showed a good tolerance profile in cats.

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Keywords: ProMeris[®]; Metaflumizone; Cat flea; Cat; Clinical field study; Fipronil

1. Introduction

Fleas are the major ectoparasite affecting cats. The main flea species found on cats is *Ctenocephalides felis felis* (Rust and Dryden, 1997; Beck et al., 2006). In Europe, fleas tend to occur on cats from spring to winter and are intermediate hosts for the tapeworm *Dipylidium caninum*, and can transmit a number of pathogens including *Bartonella henselae*. Therefore, treatment

against fleas is important to prevent both feline and human disease.

Metaflumizone is a novel insecticide in the semicarbazone class of chemistry with potent activity against fleas (Takagi et al., this volume), and no known cross-resistance to other chemistries (Salgado and Hayashi, this volume). A novel spot-on formulation containing metaflumizone (ProMeris[®] for Cats, Fort Dodge Animal Health, Overland Park, KS) applied as a single application to cats at a minimum dose of 40 mg metaflumizone/kg provides up to 6 weeks of control of fleas in laboratory studies (Holzmer et al., this volume). The objective of this study was to

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evaluate the efficacy and persistency of metaflumizone for the treatment of natural infestations of fleas in client-owned cats presented as veterinary patients in Europe. Efficacy relative to Day 0 counts was tested in comparison with a marketed reference product containing fipronil (Frontline[®] spot-on, Merial, Duluth, GA) based on flea counts at intervals following treatment. This multi-center field clinical study was conducted according to Good Clinical Practice Guidelines (VICH, 2000) in veterinary clinics in Germany and France.

2. Materials and methods

2.1. Animals

Cats presented to the participating clinics with flea infestations were enrolled in the study. To be included in the study, cats had to have ≥ 5 viable fleas. Cats were not eligible for the study if they were < 10 weeks of age, < 2 kg bodyweight, kittens being nursed, lactating cats or cats for which mating was planned. Cats with any history of apparent reactions to any spot-on parasitocidal treatment, cats with pre-existing medical and/or surgical conditions other than flea infestation, or were bathed/shampooed within 48 h before treatment or were planned to be bathed/shampooed during the study were also excluded. The animals remained with their owners under their usual housing conditions before, during and after the study.

2.2. Experimental design and methods

Sixteen veterinary clinics in four different areas (North, South, East and West) of Germany and eight clinics in three areas (Central, West Coast and South) of France enrolled patients to the study. Enrolments were done from May to November 2004, a period when flea infestations regularly occur in these geographical areas of Europe (Beck et al., 2006). Day 0 was defined as the day the animal presented to the clinic was initially identified, assessed and treated. On Day 0, prior to enrolment, the animal's details were recorded, a physical examination was performed to assess the general health of the animal, the suitability of the animal for the study was assessed, the relevant history recorded and the clinical observations including flea counts on the whole body surface, using a standardized procedure, were done. Each animal was assigned a unique identification number and informed owner consent was obtained. Ongoing flea challenge was monitored by observing

other clients presenting their pets to the clinics during the time of the study.

Only cats with ≥ 5 viable fleas were selected as primary flea patients and allocated to treatment according to a randomization list for flea households. Animals/households were allocated to treatment with metaflumizone or fipronil in the ratio of 2:1. Only households with a maximum of five animals household were enrolled: i.e., apart from the primary patient up to four additional household animals (cats and/or dogs), with a maximum of three cats, were treated. One animal was assigned as the primary patient, which was used for the efficacy assessment. Other cats (secondary animals) in the household were treated with the same product as the primary cat. Dogs were treated with a registered flea control product.

To reduce bias, the study was blinded by separating trial responsibilities. The Dispenser allocated and treated animals and the examining Veterinarian conducted the parasite counts and clinical observations. The examining Veterinarian remained blinded to treatment groups.

Flea counts were conducted using a standard flea comb, with animals combed over the entire body for at least 5 min. During the process fleas were removed from the cat and checked for viability. Parasite counts were recorded on a standardized form. In addition to Day 0, flea counts and clinical examinations were performed when the clients returned the animals to the clinic on Days 14 ± 2 , 28 ± 2 , 42 ± 2 , and 56 ± 2 . Safety of the test product was observed, documented, summarized and descriptively analysed for all cats treated based on findings of the examining Veterinarian or reported by the owner.

2.3. Treatment

Animals in both treatment groups were treated once on Day 0 according to their individual bodyweight. Following allocation, the Dispenser either treated the animal or supervised the treatment by the animal owner. Metaflumizone was administered as a unit dose, providing the recommended minimum dose of 40 mg metaflumizone/kg, according to the following weight bands: ≤ 4.0 kg, 0.8 ml; > 4.0 kg, 1.6 ml. Individual cat doses were supplied in glass vials and the appropriate dose was drawn into a suitably sized disposable syringe. The entire dose was applied using the syringe to a single spot-on the skin on the dorsal midline at the base of the skull. The fipronil spot-on was applied in a similar fashion following label directions using the commercial applicator.

Table 1

Details of cats enrolled in a multi-center field clinical study evaluating the efficacy and safety of a metaflumizone spot-on formulation for the control of fleas

	Sex no. (%)		Mean (range)		Breed no. (%)	
	Male	Female	Age (years)	Bodyweight (kg)	Pure	Mixed
Metaflumizone	99 (52.7)	89 (47.3)	4.2 (0.3–16)	4.0 (2.0–10.4)	13 (6.9)	175 (93.1)
Fipronil	50 (47.2)	56 (52.8)	5.3 (0.1–16)	4.0 (1.1–9.2)	5 (4.7)	101 (95.3)

2.4. Data analysis

Calculations and analyses were performed using SAS[®] statistical analysis software (SAS Institute Inc., Cary, NC, USA, release version 8.2). A natural logarithmic transformation $\{\ln(\text{count} + 1)\}$ was applied to flea counts prior to analysis. Geometric mean (gm) flea counts were calculated from the least square means of the analysis of variance with treatment and assessment day as variables. These were used to estimate percentage reductions of flea counts within each treatment relative to baseline (Day 0) using the following formula:

$$\% \text{ efficacy} = \frac{\text{gm Day 0} - \text{gm assessment Day}}{\text{gm Day 0}} \times 100$$

Non-inferiority of ln-transformed mean flea counts for cats treated with metaflumizone compared with those for cats treated with fipronil was assessed for each of Days 14, 28, 42 and 56 using a non-inferiority margin (delta) of 0.55 and assuming that the control product, fipronil, had a mean count of 0.90 and a standard deviation of 1.14. Within each treatment group, the ln-transformed counts of both ticks and fleas at each post-treatment time point was compared to Day 0 using a paired *t*-test.

3. Results

3.1. Animals

Sixteen practices in Germany and eight in France enrolled patients forming the study population. Enrolments were completed from May to November 2004, a period when flea infestations regularly occur in these geographical areas of Europe. In total, 294 individually identified cats were treated; these comprised 173 primary flea patients and 121 supplementary cats. The total number of cats treated was considered the “safety” population; 188 were treated with metaflumizone and 106 with fipronil. Cats were recruited from a range of geographical areas and varied living conditions, including single and multi-pet households and indoor and

outdoor accommodation. Animal details are summarized in Table 1. The distributions of hair coat lengths were similar for cats in both treatment groups (Table 2). Similarly, the proportions of cats exposed to water, shampooing or environmental insecticidal treatments, based on Day 0 information from clients, was consistent for cats from both treatment groups (Table 3).

3.2. Efficacy against fleas

Fleas were not identified to species during the study, but it was assumed that the predominant species was *C. felis felis*. The mean Day 0 flea counts were 11.28 and 10.91 fleas per cat for the metaflumizone and fipronil groups, respectively (Table 4). Based on the geometric mean flea counts, metaflumizone was non-inferior ($P < 0.05$) to the control product at all post-treatment observations (Days 14, 28, 42 and 56). Flea count reduction was 91.0%, 89.4%, 90.8% and 90.7%, respectively, for metaflumizone compared to 91.7%, 86.9%, 84.6% and 87.7%, respectively, for fipronil. The efficacy of the metaflumizone treatment was relatively constant throughout the study. Within groups, the reduction of flea counts following treatment was highly significant ($P < 0.0001$) compared to Day 0 at all time points for both metaflumizone and fipronil. Ongoing evaluation of other cats presented to the clinics during the study indicated that there was a consistent flea challenge.

3.3. Health observations

Five of the 188 animals treated with metaflumizone showed reactions that might have been related to

Table 2

Hair coat length of cats enrolled in a multi-center field clinical study evaluating the efficacy and safety of a metaflumizone spot-on formulation for the control of fleas

	Hair coat length, no. (%)		
	Long	Medium	Short
Metaflumizone	17 (9.0)	43 (22.9)	128 (68.1)
Fipronil	8 (7.6)	24 (22.6)	74 (69.8)

Table 3

Exposure to water by swimming or thorough wetting (at least monthly), shampooing or environmental parasite treatments for cats enrolled in a multi-center field clinical study evaluating the efficacy and safety of a metaflumizone spot-on formulation for the control of fleas

	No. (%)					
	Water exposure		Shampooing		Env. treatment	
	Never	Monthly	Never	Monthly	Never	Monthly
Metaflumizone	114 (99.1)	1 (0.9)	115 (100)	0 (0)	111 (96.5)	4 (3.5)
Fipronil	58 (100)	0 (0)	58 (100)	0 (0)	57 (98.3)	1 (1.7)

Table 4

Geometric mean flea counts and percent efficacy in cats following a single treatment with metaflumizone or fipronil

Study day	Metaflumizone			Fipronil		
	No.	Geometric mean flea count	Efficacy (%)	No.	Geometric mean flea count	Efficacy (%)
0	103	11.28	–	57	10.91	–
14	103	1.01*	91.0	57	0.90*	91.7
28	100	1.20*	89.4	56	1.42*	86.9
42	97	1.04*	90.8	56	1.68*	84.6
56	96	1.05*	90.7	56	1.34*	87.7

Flea counts significantly less than on Day 0 (* $P < 0.0001$).

treatment. Four cases (2.1%) showed application site reactions; two cases had alopecia and one of these also had erythema, two cases of temporary color changes of the fur were reported and one of these cases also showed hypersalivation following grooming of the application site. One case (0.5%) showed apathy. These reactions were mild and resolved with no treatment. No suspected adverse drug reactions were reported for the fipronil treatment.

4. Discussion

This field clinical study was conducted to confirm the efficacy and safety of a metaflumizone spot-on formulation for cats under normal use conditions in Europe. The study was conducted from April to November 2004 and a sustained parasite pressure was demonstrated. Other workers have reported that flea infestations are generally present in Germany from May to December (Beck et al., 2006; Beck and Pfister, 2006). Both groups were similar with regard to sex ratio, age, bodyweight, hair length and water contact, and included various breeds. Following a single application, metaflumizone was effective in reducing flea infestations for at least 56 days. Post-treatment efficacy for metaflumizone ranged from 89.4% to 91.0% and was still 90.7% at Day 56. Efficacy of the control product was similar and ranged from 91.7% on Day 14 to 84.6% on Day 42.

Treatment with metaflumizone resulted in high efficacy (>95%) when assessed at 48 h after treatment

for up to 6 weeks after treatment in controlled laboratory challenge studies in cats (Holzmer et al., this issue). Dryden et al. (2005) showed that the peak efficacy against fleas on cats for fipronil was achieved at 24–48 h after reinfestation. It has been shown that monthly spot-on insecticide treatments will provide excellent control of fleas in simulated home environments (Hutchinson et al., 1998) and when assessed in the home (Dryden et al., 1999, 2000). As the levels of control for both products remained high and constant for the entire study, flea reinfestation pressure within the household environment should have been reduced. Thus, it was likely that many of the live fleas detected at the post-treatment clinical exams in the current study were a recent reinfestation, possibly picked up within the previous 24 h outside the house from the environment when the cat was out. The flea efficacy in this study was similar to results for a field clinical study in dogs where treatment with metaflumizone resulted in consistent efficacy of around 90% for 8 weeks after treatment (Hellmann et al., this volume).

5. Conclusions

The results of this study showed that a metaflumizone spot-on administered at a minimum dose rate of 40 mg/kg was highly effective (>89.4%) in controlling existing infestations of fleas for up to 8 weeks. Metaflumizone provided similar reductions of flea counts to a commercial fipronil spot-on. The

metaflumizone treatment showed a good tolerance profile in cats.

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