

Papers

Evaluation of spinosad for the oral treatment and control of flea infestations on dogs in Europe

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The novel ectoparasiticide spinosad is a naturally occurring mixture of spinosyns A and D formed during a fermentation process. The spinosyns are tetracyclic macrolides with a unique ring system. Their mode of action differs from that of other commercially available insecticides. Laboratory and field trials were conducted to evaluate the use of spinosad in a chewable tablet at a dose range of 45 to 70 mg/kg for the treatment and control of flea infestations on dogs in Europe. Laboratory studies with artificially infested dogs confirmed persistent activity against *Ctenocephalides felis* of higher than 99 per cent at three weeks post-treatment with values of 96.5 to 97.8 per cent at four weeks. Two multicentric field trials with naturally infected client-owned animals in five European countries used selamectin as comparator. Monthly doses were given during the summer when many homes were heavily infested. Households with spinosad-treated dogs showed cumulative benefits with flea burdens reduced by about 97 per cent at 14 and 30 days and by 99.6 per cent at 60 and 90 days. Corresponding figures for selamectin were significantly lower ($P < 0.05$) at all time points: between 88.5 and 91 per cent at 14 and 30 days, then 97.8 and 98.2 per cent at 60 and 90 days. Thus, the performance of spinosad compared favourably with that of the established reference product.

DESPITE the introduction over the past 10 to 15 years of a number of highly effective long-acting topically applied pulicidal compounds such as imidacloprid, fipronil, selamectin, pyriprole and metaflumizone (Dryden 2009), fleas continue to be a frequent cause of discomfort and canine disease throughout much of Europe (Farkas and others 2009). The so-called 'cat flea', *Ctenocephalides felis*, feeds on humans as well as on a variety of domesticated and wild animals, and is the commonest species found on dogs. Fleas mostly cause minor irritation, unless present in large numbers, but some dogs may develop hypersensitivity reactions (flea-allergic dermatitis) of greater or lesser severity. Fleas may also transmit other potential pathogens such as the tape-

worm, *Dipylidium*, and microorganisms including some *Bartonella* and *Rickettsia* species (Rolain and others 2003, Shaw and others 2004). Cat fleas have shown a propensity to develop resistance to earlier insecticidal classes, such as cyclodienes, carbamates, organophosphates and pyrethroids. Extending the longevity of currently effective therapies should be a major goal of the veterinary community (Rust 2005). Thus, there is a continuing need to develop improved flea-control methodologies and to expand the chemotherapeutic options available to the veterinarian for this purpose.

The latest addition to the range of commercially available long-acting pulicides is spinosad (Comfortis, Elanco) which is characterised by oral rather than topical administration and a rapid speed of kill (Blagburn and others 2010). Spinosad is a naturally occurring mixture of spinosyns A and D formed during a fermentation process employing the soil-dwelling actinomycete, *Saccharopolyspora spinosa*. Structurally, spinosyns are tetracyclic macrolides with a unique ring system. They exhibit a novel mode of action primarily involving nicotinic acetylcholine receptor binding sites (nAChRs) that are distinct from those targeted by other insecticides (Sparks and others 2001). The outcome is disruption of the flea's nervous system. A secondary effect on γ -aminobutyric acid (GABA) may potentiate this pulicidal activity. The low mammalian toxicity associated with spinosad is likely to be due to a lack of homology between insect and mammalian nicotinic and/or GABA receptors. Spinosad is presented for flea-control as a 'chewable' tablet (ie, a tablet that is efficacious whether swallowed whole or after being chewed or bitten). Preliminary dog studies indicated that effective flea-control over a four-week period could be obtained with dose rates of 30 mg spinosad/kg bodyweight or above (Snyder and others 2007). A minimum dose of 45 mg/kg was selected for European laboratory studies to ensure compliance with all local regulatory requirements (EMA/CVMP 2007). As is the case with all medicines presented in tablet form, any combination of tablet sizes has to cover a range of bodyweights and tablet strengths are therefore designed to provide dosag-

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es within strictly defined limits. This paper describes laboratory and field investigations evaluating a dose range of 45 to 70 mg spinosad/kg bodyweight for the oral treatment and control of flea infestations on dogs in Europe.

Materials and methods

Three laboratory and two multicentric field studies are reported. They complied with internationally accepted guidelines and standards for trial design and animal welfare (EMA/CVMP 2000, 2007, Marchiondo and others 2007) as well as all relevant local regulations and ethical requirements.

Laboratory studies

Study design

Laboratory investigations included a preliminary dose-demonstration study using unformulated spinosad powder and two dose-confirmation studies with chewable tablets. All were designed as randomised complete block studies and partly blinded to minimise the risk of unintentional bias. The dose-confirmation studies were conducted independently at separate locations.

Animals and infestations

Individually housed laboratory beagles with bodyweights between 10 and 17 kg were used. As part of the allocation procedure, all dogs were infested with 100 newly emerged unfed fleas about one week before the scheduled treatment date to account for variation in individual susceptibility. Insecticidal activity was evaluated by a similar application of fleas on the days indicated for each study. Fleas were counted and removed 48 hours after each infestation. To do this, dogs were combed systematically with a fine-toothed comb until no more fleas were detectable. Personnel conducting flea-counts were unaware of which treatment had been given.

Treatment

An earlier observation (Snyder and others 2007) had suggested that feeding around the time of dosing improves spinosad bioavailability. On the day of treatment, therefore, all dogs were offered 25 per cent of their daily canned ration no more than 30 minutes before they were dosed. Control dogs received a placebo identical to the spinosad presentation but without an active ingredient. To ensure that the whole dose was swallowed, the capsule or tablet was placed over the back of the tongue with a small volume of water. The remainder of the daily meal was given after dosing.

Statistical analysis

Before each analysis of results, a logarithmic transformation ($\ln(\text{count}+1)$) was applied to the live flea-counts for each animal at each scheduled time point. This transformation addressed the skewness of the data and also allowed for zero counts. Back-transformed geometric means were calculated as $e^{\bar{x}}-1$, where $\bar{x}$ was the arithmetic treatment mean of log-transformed counts at a given time point. Efficacy based on the reduction of flea-counts attributable to treatment was calculated using the following formula:

$$\text{Efficacy (per cent)} = \frac{C-T}{C} \times 100$$

Where, C is the geometric mean of the flea-counts of the control group and T is the corresponding geometric mean for the treated group.

Preliminary study

The preliminary dose-demonstration study (study 1) employed two groups of six dogs, each comprising four males and two females. The purpose was to confirm the residual insecticidal efficacy of spinosad at the proposed European minimum dose rate of 45 mg/kg. For this, each dog was treated on day 0 with an exact dose, based on its bodyweight of unformulated spinosad powder in a gelatine capsule. Control dogs received empty capsules. Fleas were applied on days 21 and 28.

Dose-confirmation studies

The first dose-confirmation trial was conducted in Germany (study 2) and included two groups of eight dogs with equal numbers of males

and females in each. The second, in France (study 3), was similar but with an additional female in the control group bringing the total of untreated dogs to nine. Whole spinosad tablets (Comfortis, Elanco) or placebo tablets were given on day 0. Treated dogs weighing less than 12.5 kg received a tablet containing 560 mg spinosad, whereas those over this weight received 810 mg spinosad. Fleas were placed on the animals on the day before treatment (day -1) in the French study and on days 7, 14, 21 and 28 in both studies.

Field studies

Study design

Field investigations included a one-month trial (study 4) covering five European countries (UK, Netherlands, France, Germany and Italy) and a three-month trial (study 5) confined to France but spanning both Atlantic and Mediterranean climatic zones. Each was a blinded positive-control multicentre study using a randomised complete block design. Data collection was standardised using preprinted forms and questionnaires. The experimental unit was the household represented by one dog. Ethical considerations did not permit the use of negative (untreated) controls, and thus spinosad treatments were compared with an established reference product. Because no alternative long-acting oral pulicide was commercially available, selamectin (Stronghold, Pfizer) was selected for this purpose. Although chemically unrelated and topically applied, selamectin (like spinosad) is a long-acting pulicide with systemic activity (Sarasola and others 2002). As the two products are so different in formulation and presentation, their identity could not be masked, but trial blinding was achieved by ensuring that personnel conducting flea-counts were unaware of which treatment had been given. In accordance with current guidelines, the randomised allocation procedure allowed one positive control for every two spinosad test homes.

Animals

For enrolment, dogs at first inspection had to be naturally infested with at least 10 fleas but otherwise healthy, over six weeks old and with a minimum bodyweight of 1 kg. They were not accepted if intended for breeding within six months or if any flea treatment had been used within a specified time period (dependent on the nature of the product used), or if their disposition or hair-coat precluded accurate flea-counting. Cooperating dog owners were fully informed and provided a written consent.

Treatments

Spinosad-treated dogs received an appropriate combination of whole chewable tablets to provide a dose within the range of 30 to 90 mg/kg (although only animals receiving 45 to 70 mg/kg were used for efficacy evaluation, see statistical analysis section below). Their owners, after appropriate instruction, administered the treatments at home together with food. Selamectin was applied as per label instructions (ie, topically as a spot-on preparation to provide a minimum dose of 6 mg/kg). All dogs in multi-pet homes were treated with the same product. Cats in participating households received selamectin irrespective of the dog treatment (since no spinosad formulation suitable for cats was available and flea-control in the home depends on all pets being treated). The use of any other medicament, shampoo, food supplement, environmental treatment etc containing any ingredient efficacious against fleas was prohibited during the course of the trial.

After the initial flea-count and allocation, recruited dogs were dosed on day 0 in the one-month study (study 4) and at monthly intervals on days 0, 30 and 60 in the three-month study (study 5).

Flea-counts

A standardised flea-combing procedure taking at least 15 minutes was performed by trained practice staff using a separate flea-comb for each dog. Only live, viable fleas were recorded (ie, those demonstrating normal movement and behaviour, with an ability to maintain an upright posture and cling onto hair). In study 4, flea-counts were performed on days 14 and 30 (with a discretionary period of ± 2 days to encourage owner compliance) and on days 14, 30, 60 and 90 ($\pm$ three days) in study 5. Observations were completed before dosing on treatment

days. In the case of multi-pet homes, flea-count data were collected from only one designated dog.

Statistical analysis

The prescribed spinosad dosage used in these trials was based on results from early studies (Snyder and others 2007) and as a consequence spanned a broader dose range (30 to 90 mg/kg) than that subsequently selected for European registration (45 to 70 mg/kg). To fulfil the objective of the current publication, therefore, data from spinosad-treated dogs receiving less than 45 mg/kg or more than 70 mg/kg were rejected from the analysis. This constrained the numbers of eligible spinosad-treated dogs to 93 (of 197) and 43 (of 130) in studies 4 and 5, respectively. These restrictions did not affect the statistical power or validity of the analysis. The full set of positive control (selamectin) dogs was kept for comparison.

In the absence of negative (untreated) controls, efficacy values were calculated by comparing post-treatment flea-counts with baseline data collected immediately before the first treatment. For reasons outlined above for the laboratory studies, geometric means were used for this purpose. Further analysis on the log-transformed (flea-count+1) data used a repeated measures mixed effects linear model for values on successive observation days. In addition to estimating reduction in flea populations on treated dogs, the proportion of dogs in each treatment group on which no fleas could be found (the 'zero-flea' percentage) was also recorded.

Results

Laboratory studies

In all cases, pretreatment observations confirmed that flea infestations could be established on all animals in sufficient numbers to allow valid statistical analysis. Feeding and treatment procedures were completed without problem and all animals received their full dose, which in the dose-confirmation trials ranged from 45.9 to 54.0 mg/kg. Efficacy values for each observation-point in the three studies are displayed in Table 1. Flea populations established on dogs in study 3 one day before treatment were completely eliminated. Residual efficacies in all three studies were greater than 99 per cent up to three weeks post-treatment, while day 30 values of 96.5, 96.5 and 97.8 per cent were recorded in studies 1, 2 and 3, respectively.

Field studies

The clinical phase of each field study was completed between May and November and encompassed a wide range of geographical, social and climatic regions. Data from 34 veterinary clinics qualified for inclusion in study 4, and from 21 clinics in study 5. The test population in study 4 comprised female and male dogs in almost equal proportions (54.5 v 45.5 per cent). They belonged to no fewer than 52 breeds. Longhaired varieties were, however, in a minority (9.6 per cent). Bodyweight ranged from 1.3 to 65 kg and age from seven weeks to 17 years. Homes with a single dog, with more than one dog (but no cat) or with at least one cat were almost equally represented (32.6, 37.9 and 29.5 per cent, respectively). Most (82.7 per cent) lived partly or fully outdoors. Study 5 was similarly diverse, although a larger proportion (69.3 per cent) was kept indoors.

Flea populations at the time of recruitment were often substantial and were comparable between treatment groups. The largest initial flea infestations recorded for spinosad- and selamectin-treated groups, respectively, were 560 and 229 in the first trial; they were 437 and 394, respectively, in the second trial (Table 2). Pretreatment geometric mean flea-counts for spinosad- and selamectin-treated groups, respectively, were 36.7 and 29.7 in study 4, and 40.7 and 33.5 in study 5.

At both 14 and 30 days post-treatment, flea burdens of spinosad-treated dogs were reduced by about 97 per cent compared with pretreatment values (Table 2), while corresponding figures for selamectin were significantly lower (90.7 and 88.5 per cent on day 14; 89.4 and 91.0 per cent on day 30 in studies 4 and 5, respectively). At the end of the second and third months, reductions of 99.6 per cent were recorded for the spinosad group, while selamectin values were again significantly lower at 97.8 and 98.2 per cent on days 60 and 90, respectively.

The proportion of spinosad-treated dogs on which no fleas could be found (Table 2) varied during the first month from a low of 39.5 per cent (study 5, day 14) to a high of 59.1 per cent (study 4, day 14). Corresponding figures for the selamectin animals were 28.6 per cent (study 5, day 14) to 34.1 per cent (study 4, day 30). Following the second monthly dose, the figures for spinosad and selamectin increased to 77.5 and 62.9 per cent, respectively. By day 90, they had become significantly different ($P=0.042$) at 85 and 67.1 per cent, respectively.

Discussion

Laboratory studies are usually designed to isolate and define single aspects of the biological activity of an experimental compound. They provide essential building blocks for knowledge and understanding but rarely do they fully reproduce or reflect the complexities of natural disease. In this respect, domestic flea infestations present a particularly challenging therapeutic problem (Rust and Dryden 1997). Only a small part of the total flea population resides on the host animal. In much greater abundance are off-host life cycle stages such as eggs, larvae, pupae and newly emerging adults found in locations such as carpets, furniture and bedding. Flea-control therefore depends on the overall impact of veterinary and other interventions on the dynamics of this ecological system. Modern veterinary pulicides can influence this process in a number of ways depending upon their particular biological characteristics, the nature and spectrum of which vary between products. Such attributes can include their short-term effect on adult fleas (knockdown), longer-term residual activity, speed of kill,

TABLE 1: Laboratory studies: percentage reduction in flea-counts comparing spinosad-treated dogs with placebo-treated controls 48 hours after each infestation

Study	Formulation	Actual dose given mg/kg	% Reduction in flea-count measured on day					
			1	9	16	23	30	
1	Powder	45	-	-	-	99.8	97.8	
2	Tablet	45.9-54.0	-	99.9	100	99.4	96.5	
3	Tablet	48.2-53.0	100	100	100	99.1	96.5	

TABLE 2: Field trial data: percentage reduction in flea-counts of spinosad and selamectin-treated dogs (compared with pretreatment values on day 0) and the proportion of flea-free dogs at each observation day

Treatment*	Total number of dogs	Number of fleas on day 0†	% Reduction in flea-counts on day				% Dogs with zero fleas on day			
			14	30	60	90	14	30	60	90
Study 4‡										
Spinosad	93	36.7 (11-560)	97.5	97.2	-	-	59.1	54.5	-	-
Selamectin	93	29.7 (10-229)	90.7	89.4	-	-	33.7	34.1	-	-
P values§			0.001	0.003	-	-	0.001	0.006	-	-
Study 5¶										
Spinosad	43	40.7 (10-437)	97.3	97.4	99.6	99.6	39.5	50.0	77.5	85.0
Selamectin	71	33.5 (10-394)	88.5	91.0	97.8	98.2	28.6	31.4	62.9	67.1
P values§			<0.001	0.005	0.01	0.035	NS	NS	NS	0.042

* Spinosad 45 to 70 mg/kg; selamectin 6 to 11.8 mg/kg

† Geometric mean and range

‡ Treated day 0

¶ Treated days 0, 30, 60

§ Comparing spinosad and selamectin groups

NS Not significant ($P>0.05$)

anti-feeding potential, repellency and larvicidal effects (Carlotti and Jacobs 2000). Furthermore, these properties can be modified by factors such as formulation, dose and method of application. Consequently, field studies play a particularly important role in evaluating prospective flea-control agents as they come closest to encompassing the full scope of these ecological and therapeutic complexities.

Effective flea-control is a three-stage process (Carlotti and Jacobs 2000). First, the removal of fleas from an already infested host provides relief from discomfort and aids the resolution of skin lesions due to self-trauma or allergy. Secondly, the animal must be protected from re-infestation since the household environment is likely to be contaminated and therefore a continuing source of hungry host-seeking fleas. Thirdly, the reservoir of off-host life cycle stages must be eliminated as this is the only way a long-term solution can be provided. Traditionally, this was achieved by the direct application of chemicals onto flea development 'hotspots' around the home (Rust and Dryden 1997). More recently, however, this approach has been largely superseded by long-acting animal treatments that halt the deposition of viable flea-eggs. With no new eggs entering the system, the domestic reservoir of developing fleas becomes progressively depleted and is eventually driven towards extinction (Dryden 2009).

Under most household conditions, fleas originating from eggs deposited before the start of a control programme will have completed their development and emerged from their cocoons within three to five weeks, but this process can in some cases be delayed by up to 174 days (Dryden and Rust 1994) and may influence the results of clinical trials. Nevertheless, in the current field investigation, a 99.6 per cent reduction in flea burdens on dogs was observed in spinosad households 60 days from the start of the monthly dosing programme and the 'zero-flea' data suggested that fleas had been eliminated from up to 85 per cent of these homes by day 90 (Table 2). This compared favourably with the selamectin controls in which a 97.8 per cent reduction in flea-count was recorded at day 60 and a 'zero-flea' value of 67 per cent at day 90.

These investigations were conducted over the summer season in a variety of climatic regions including warm, humid areas favouring flea reproduction. Thus, these results were obtained at a time when flea populations would normally be increasing in magnitude. Indeed, the day 14 zero-flea figures indicate the presence of heavy challenge in many of the households in the early part of the two studies (Table 2) with evidence of re-infestation taking place on 41 and 60 per cent of spinosad dogs, respectively, and on 66 and 71 per cent of the selamectin groups. Nevertheless, the overall number of fleas on the animals at day 14 had been reduced by 97 per cent in the case of spinosad and by about 90 per cent for selamectin indicating a high level of protection in the face of continuing re-infestation. Similar results have been reported from a comparable trial encompassing 14 sites in the USA and two in Canada (Robertson-Plouch and others 2008).

The high-performance level of spinosad under challenging clinical situations in both European and North American field trials can be ascribed to the summation of its inherent pulicidal attributes, including 'knockdown', duration of activity, speed of kill and the resultant impact of these on flea-egg output. At dose rates of 30 mg/kg or more, the 'knockdown' effect of spinosad against a previously established flea population is virtually 100 per cent (Snyder and others 2007, Blagburn and others 2010). Thereafter, a high level of residual protection against re-infestation is maintained for a month (Snyder and others 2007). In this study, where dose rates in individual dogs ranged from 45 to 54 mg/kg, values higher than 99 per cent were recorded up to day 23 and of 96.5 per cent at day 30 (Table 1). The speed at which spinosad kills fleas was investigated by Blagburn and others (2010) using a dose rate of 30 to 60 mg/kg. Mortality was evident as early as 30 minutes after treatment with a significant reduction (64.2 per cent, $P < 0.05$) at one hour. By two hours, efficacy had increased to 85.8 per cent and had reached 100 per cent by four hours. This is of significance in control programmes as newly acquired fleas must be killed before they start to lay eggs, if recontamination of the household environment is to be avoided. To measure the effect of spinosad-treatment on flea-egg production, Blagburn and others (2010) collected eggs dropping from treated dogs and untreated controls that had been infested with fleas at intervals over a one-month period. They estimated that treatment had reduced the number of eggs falling to the ground by at least 99.8 per

cent. Extrapolating this result to a domestic setting, monthly spinosad treatments would therefore be expected to make a major contribution towards the long-term objective of eliminating the environmental reservoir of off-host life cycle stages. Complementary interventions such as household vacuum cleaning, particularly of potential hotspots, are of course invaluable adjuncts for accelerating progress towards this goal.

The fast onset of flea mortality following oral dosing observed by Blagburn and others (2010) can be explained by rapid absorption of spinosyns A and D from the canine gastrointestinal tract, with maximum plasma concentrations occurring about two to four hours after treatment (Anon 2007). The systemic activity of spinosad has other potentially beneficial consequences. For example, newly acquired fleas start to feed within minutes of jumping onto their host (Dryden and Gaafar 1991, Cadiergues and others 2000) and may thereby assimilate a lethal dose of a systemic pulicide more quickly than by absorption of a topical contact insecticide through the cuticle (McCoy and others 2008). Furthermore, as spinosad is not known to be present in sebum, shed hair or skin flakes (Blagburn and others 2010), direct transfer from treated animals onto animal handlers or into the household environment is unlikely.

In conclusion, the rapid absorption and fast speed of kill of spinosad ensure that infested dogs respond quickly to treatment and that fleas acquired subsequently are killed before they start to lay eggs, thereby breaking the flea life cycle in contaminated households. A monthly dosing programme using client-owned dogs, many of which would have been kept under conditions of heavy natural challenge, reduced parasite burdens on dogs by 97 per cent during the first month and drove the flea population close to extinction in the majority of homes within 60 days. In comparative field studies, efficacy values for spinosad were higher than those obtained for the reference product, selamectin. Thus, laboratory and field trials have confirmed that spinosad chewable tablets administered to dogs at a dose rate of 45 to 70 mg/kg are highly effective for the treatment and control of flea infestations.

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