Flea control in flea allergic dogs and cats

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Summary

Flea allergy dermatitis (FAD) remains the most common allergic skin disease of dogs and cats, although its frequency varies according to geographical location. Despite the availability of safe, effective products, treating FAD remains a challenge. This challenge should be more readily overcome once both practitioner and owner(s) are entirely convinced of the diagnosis. The main difficulties and pitfalls facing the practitioner are described. Treatment requires appropriate knowledge of the flea life cycle and flea-related biology, and understanding of the mode of action of the relevant flea control products. An integrated approach to treatment should be adopted, involving all the players in the flea life cycle - the FAD patient, all in-contact pets, and the environment. Each case must be customised, with effective flea control products used in combination with cleaning measures such as steaming, vacuuming and regular grooming.

Introduction

Flea allergy dermatitis (FAD) remains the most common allergic skin disease of dogs and cats, although its frequency varies according to geographical location. The past twenty years have brought important advances in flea biology as well as better insecticides [1]. Nevertheless, flea control in general, and more specifically in dogs and cats with FAD, remains a real challenge for vets.

This paper will be divided into four sections. The first will focus on flea biology on which flea control programmes are based. In the second, the main difficulties and pitfalls facing practitioners will be described. The third section will outline the various active ingredients and formulations currently available. The last chapter will consider specific flea control recommendations.

Flea biology and flea control

Various aspects of flea biology may be useful in improving flea control and/or understanding failure or inadequacy of flea control programmes.

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The vet should ensure that the client understands these relevant basic principles of flea biology.

Host phase

The adult stage of both Ctenocephalides felis felis and Ctenocephalides canis (also called cat flea and dog flea respectively), lives permanently in the hair coat of its host. Exchanges between animals are possible but limited, and should not be considered the main source of infestation. Fleas have a tendency to leave their host when the host’s temperature decreases (e.g. death, anaesthesia), when the species is not well adapted to the host (e.g. C. canis in cats) or when the on host population is extremely high [2].

Early onset of blood feeding

Once the adult (imago) has colonised a new host, it will take its first blood meal very rapidly. About 25% of cat fleas start to feed within 5 minutes of being free in the coat and about 97% have taken a blood meal within 1 hour [3]. Although C. canis takes its meal more slowly, 72.5% of fleas begin blood feeding within one hour [4]. The mean duration of the first blood meal, evaluated on individual fleas confined on animals, has been found to be 25± 18 minutes in females C. felis and 11± 8 minutes in males C. Felis [3]. It was significantly shorter (5 and 6 minutes, respectively for C. canis) [4]. These data demonstrate the difficulty if not the impossibility of preventing newly emerged fleas from taking a blood meal and hence injecting their saliva.
Blood feeding and lifespan

Although it is clearly established that blood-feeding is necessary for mating and laying viable eggs [2], the number of blood meals and their frequency remain unknown. It is thought that fleas will continue to bite and have blood meals until they die. The lifespan of *C. felis felis* is usually considered to be between 2 and 3 weeks. Under experimental conditions, mean survival of *C. canis* in the canine coat was 8.6 days [5]. Clearly, flea lifespan depends highly on the level of grooming (by the animal itself or the owner). Survival of 250 unfed fleas of both species was evaluated in the environment at 19°C and 27°C (RH 70%). Mean survival of 50% of *C. canis* was 15.9 days (19°C) and 9.0 days (27°C). Under similar conditions, mean survival of *C. felis* was 11.7 days (19°C) and 9.6 days (27°C). After 48 hours on a dog, mean survival of females was 7.9 days (19°C) and 4.8 days (27°C) for *C. canis* and 4.9 days (19°C) and 3 days (27°C) for *C. felis*. Survival of males was shorter [5].

First eggs

Female fleas lay their first eggs between 24 and 36 hours after colonising a host. Eggs are laid in the coat and subsequently fall to the ground. They are then susceptible to insect development inhibitors (IDIs) applied on the coat or on the ground, as well as insecticidal products. Egg production reaches a peak (around 15-20 eggs per day) during the second and third weeks and then decreases, but a female will lay eggs until it dies. Cat flea egg production usually peaks during the night, coinciding with normal sleep periods for indoor pet dogs and cats [6], hence a higher density of immature stages in animal resting places, including bedrooms. Around areas such as sofas and beds, where pets jump and play, eggs and flea faeces will be more easily dislodged from the haircoat [6].

Environmental phase and factors affecting egg production

Once on the ground, eggs require favourable environmental conditions (humidity and temperature) to develop further. Ideal conditions for the life cycle of the cat flea (relative humidity of 70% and a temperature of between 20 and 30°C) are provided by a modern home environment. The environmental phase has major implications in control because larval and pupal stages develop there and because pupae remain dormant in the environment for an extended period of time.

Larval instars

The first-instar larvae hatch from eggs in the pet’s immediate environment. They then tend to move to the base of the carpet, not travelling far from where they hatched. They search for suitable food, particularly dried blood faeces [6] but also other debris including non-viable flea eggs [7]. The second-instar larvae tend to search more widely for food and darker areas where they are less likely to be disturbed. They tend to move away from carpets, making vacuuming, which only removes 15-27% of the larvae, a rather ineffective procedure. However, regular vacuuming of pet resting places can remove 90% or more of flea eggs as well as flea faeces [6].

Pupal stage

The third-instar larva becomes a pupa encased within a cocoon formed out of various bits of environmental debris stuck together. Pupae are often found in well-protected areas such as the back of carpets, skirting boards and cushion seams. Inside, the future imagos remain dormant for several months (the so-called “pupal window”) until stimulated to hatch by triggers such as vibrations, increased carbon dioxide levels and/or temperature changes. Pupae are resistant to freezing, desiccation, insecticides and IDIs.

Imago

Once stimulated, the imago tears open the cocoon, probably as a consequence of its agitated movements, and jumps onto the first mobile, warm “object”, usually an animal. The young, unfed adult is susceptible to adulticides and IDIs. As stated earlier, the unfed flea survives longer in the environment than fed fleas. The entire life cycle can be completed in 13 to 14 days under optimal conditions but can take up to 7-9 months.

Preventing a new life cycle would require killing all the adults in the first 24-36 hours of infestation and/or applying an IDI either to the adult or to the immature stages before pupa formation. Vacuuming is not very effective due to the mobility and positive geotaxis of the larvae. Although immature stages concentrate in rooms or areas where animals spend most of their time, it is crucial to take into account places visited infrequently or visited by other animals including wildlife.

Main difficulties and pitfalls

**Convincing the owner and customising flea control measures**

Surprisingly, one major difficulty in FAD control is convincing the owner (and sometimes the referring practitioner) that FAD is the correct diagnosis. It is rather common to be faced with owner disbelief or scepticism. Because fleas are not seen by the owner, and their presence is difficult to prove on animals with FAD, the owner is sometimes absolutely convinced that fleas cannot be the cause of his/her pet’s dermatitis. Some people associate fleas with a lack of hygiene and cannot accept that their pet(s) might have fleas. Other people, who recognise fleas in dogs to be common, doubt that their pet would present with a flea-related skin disease when other pets with fleas do not have a skin problem? Furthermore, why should pruritus be so severe if only a few fleas are present? Owners may be sceptical because they think, or have been told, that they are doing everything they can to kill fleas and/or that they have used the wonder product.

Clinical features, at least in dogs, may help to convince a sceptical owner. These include a typical dorso-lumbar distribution pattern extending to the tail base, perineum and medial/caudal thighs, and crusted papules in the umbilical fold (especially in male dogs). The presence of fipropuritic nodules is also highly suggestive. The client might accept the diagnosis more readily if given clear and simple explanations about both allergy in general and flea allergy in particular. Emphasising the difference between flea infestation and flea allergy, and outlining the role of flea saliva and therefore that of flea bites is important. Describing the life cycle in relation to the pet’s individual circumstances may help the owner to understand why fleas are still present. Additional
testing and strict trial flea control for 6 weeks might finally convince the owner.

Once convinced, the owner needs guidance and motivation. Again, a clear explanation of the flea life cycle combined with information on the way products work is usually helpful. Demonstrating how to apply the product(s) correctly is recommended; a small area on the skin of the back of the neck could be shaved to ensure that a spot-on formulation is applied onto the skin and not in the fur.

The therapeutic regimen should always be customised, necessitating a thorough patient history and details of the owner’s circumstances.

In-contact animals and premises

All the in-contact animals should be treated, albeit less strictly perhaps that the patient with FAD. Cats, especially, are easily forgotten either because they live outdoors or because they may not be around when it is time to treat the dog(s). Cats can also be difficult to medicate and are sometimes not considered by owners to be part of the problem. All areas regularly visited by the pet with FAD (including cars and sheds) should be treated with a suitable product at an appropriate frequency. Visiting the pet with FAD (including cars and sheds) should be treated with a suitable product at an appropriate frequency. Visiting infested places can re-introduce fleas (mainly immature stages which can develop and lead to delayed re-infestations but possibly also adults) in a well-controlled household. Similarly, visiting infested places can trigger a flare. When such possibilities cannot be avoided, strict preventive treatment, similar to a trial therapy regimen, should be recommended.

Maintaining consistency of flea control

After a while, particularly when there is clinical improvement, attention given to flea control tends to flag. However, this must not be allowed to happen. The practitioner and/or well-trained nurses from the practice must regularly emphasise the importance of consistent flea control. Reminders can be sent, using modern communication forms (text messages, Multimedia Messaging Services on mobile phones, emails). These are sometimes offered free of charge by pharmaceutical companies.

Efficacy of ectoparasiticide [8]

Controlled studies are advocated to assess the efficacy of flea control products. Classically, efficacy is determined by comparing parasite numbers on groups of treated and control animals after experimental infestations. Fleas are deposited 48 to 72 hours before the application of a product to be assessed. Immediate therapeutic efficacy is evaluated 24 or 48 hours post-treatment by combing off and counting the surviving fleas. Parasite counts 24 or 48 hours following subsequent infestation(s) at 7-day intervals are used for residual efficacy calculations. Residual efficacy is evaluated by re-infecting the animals in each study. A threshold of 90 or 95% efficacy is required. Most products with a European licence have a 95% efficacy threshold 48 hours after infestation. Even if a product is applied according to the manufacturer’s recommendations, 100% efficacy should not, therefore, be expected. Furthermore, efficacy tends to decrease with time.

Swimming, bathing and excessive grooming

Dogs that swim or bathe regularly should receive systemic treatment (e.g. nitenpyram once daily or every other day, selamectin once monthly) as swimming or bathing degrades the efficacy of topical products. Spinosad, a new oral, beef-flavoured tablet for dogs, not yet available in Europe, would also be a product of choice as it kills fleas rapidly and remains effective for one month after application. Cutaneous inflammation, hyperhydrosis, cornification disorders (primary and secondary) and excessive grooming should be considered when applying a topical flea product. Not only may the product irritate the skin but its diffusion may also be impaired by the skin changes. Excessive grooming might reduce the amount of insecticide present on the skin thereby reducing or delaying its efficacy.

Over-the-counter products

Extensive and long-term flea control measures require considerable effort and expense. This can produce a progressive reduction in compliance, and may also explain why over-the-counter (OTC) products are sometimes preferred by owners. Most OTC products do not have the efficacy, residual activity or safety profile of the veterinary products. With time, substitution of OTC products could lead to poor control of FAD, owner frustration or even suspicion of resistance.

Active ingredients and formulations

Neonicotinoids

This class of insecticides was developed for crop protection and subsequently found to be highly effective for flea control in dogs and cats, with an excellent tolerance. Imidacloprid (Advantage®, Advantix®, Advocate® - Bayer Health Care), nitenpyram (Capstar® - Novartis SAS) and dinotefuran (Vectra 3D - Summit VetPharm, unavailable to date in Europe) are the active ingredients available for pets.

Imidacloprid has a high affinity for the nicotinic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) in insects. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death of the parasite. It is only available as a spot-on with surface action. It is effective against adult fleas, requiring 8 hours of contact [9-11]. It also has, in common with most insecticidal products, a larvicial effect [12, 13]. Combination with permethrin is likely to enhance its speed of action [14, 15].

Nitenpyram is a fast-acting, orally administrated flea treatment. Like imidacloprid, it acts on the nicotinic acetylcholine receptor channel. It is readily absorbed, with peak plasma levels reached within 30 minutes and a half-life of about 8 hours [16, 17]. First signs of efficacy are seen 15 minutes or more after infestation. Fleas are dislodged after 30 minutes, and within 6 hours, over 95% are killed. The effect is prolonged for 24-48 hours [17, 18].

Dinotefuran is a third generation neonicotinoid; dinotefuran was synthesised with acetylcholine as the lead compound whereas imidacloprid was based on nicotine. It is also a fast-killing insecticide, effective for 30 days following application [19]. It is
available in the US as a spot-on. For dogs, it is combined with pyriproxyfen and permethrin, and for cats with pyriproxyfen only.

**Phenylpyrazoles**

Introduced in Europe in 1994, fipronil has been a market leader ever since. First available as a spray (Frontline® spray – Merial), fipronil later became available in a spot-on formulation (Frontline® spot-on, Frontline® Top spot – Merial) eventually being combined with methoprene, still as a spot-on (Frontline® Combo, Frontline® Plus – Merial). More recently, pyriprole from the same chemical group has become available as a spot-on (Practic® - Novartis). Now that fipronil’s patent has expired, generic products have appeared on the market (e.g. Effipro® - Virbac). Phenylpyrazoles block the gamma-aminobutyric acid (GABA)-gated chloride channels of neurons in the central nervous system, sharing a common binding site with cyclodienes. Fipronil also binds to two different glutamate-gated chloride channels [20, 21]. Efficacy of fipronil was evaluated in dogs [22] and cats [23] with FAD. The 10%-fipronil solution, applied monthly three times, reduced flea counts on day 90 by 98%. Pruritus was reduced or eliminated in 84% of dogs [22]. The same formulation, applied monthly to cats with FAD, reduced flea counts by 94% on day 90 with pruritus reduced or absent in 78% of cats [23]. In a study comparing efficacy of selamectin, imidacloprid and fipronil in dogs experimentally infested with both Ctenocephalides felis and C. canis, the efficacy of fipronil, 48 hours after each infestation, was 100%. This persisted for 35 days after one application [24]. In studies investigating the efficacy of a single application of a 12.5% pyriproxyfen spot-on formulation, persistence of the active ingredient was assessed after repeated washing and shampooing. Neither shampooing 24 hours post-treatment nor weekly washes altered the efficacy which was 99.8-100% and 100%, respectively, for 30 days [25].

**Avermectins**

Selamectin (Stronghold®, Revolution® – Pfizer) is believed to bind to glutamate-gated chloride channels in the parasite’s nervous system, increasing permeability and allowing the rapid and continued influx of chloride ions into the nerve cell. This inhibits nerve activity thereby causing paralysis [26]. Selamectin is applied topically, is rapidly absorbed through the skin, and is distributed via the blood [27]. It has activity against both internal and external parasites. Several studies have been published supporting its efficacy against fleas [10, 12, 24, 28-32]. Topical application was over 98% effective after 36 hours in dogs and 24 hours in cats [31, 32]. In dogs, mean efficacy, 3 and 8 hours after treatment, was 39.7 and 74.4%, respectively [11]. A study performed in dogs and cats with FAD housed in flea-infested, simulated home environments [33] and a multicentre field trial performed in dogs [34] both showed a significant reduction in clinical signs of FAD in dogs and cats after two applications, one month apart. The multicentre study did not show any difference between the group treated with fipronil and the group treated with selamectin. Improvement was observed after two weeks and clinical signs had almost resolved after two months [34].

**Pyrethrins and Pyrethroids**

These products cause spontaneous depolarisation, augmented neurotransmitter secretion, and neuromuscular blockade by sodium and potassium ion transport disruptions in nerve membranes. Action is extremely rapid, but paralysed insects can also recover rapidly. Natural pyrethrum is extracted from chrysanthemum flowers and notable for its rapid but brief action and relatively good tolerance in dogs and cats. Synthetic pyrethroids are pyrethrum-like compounds with greater potency and residual effects. They are, however, toxic in cats. This is especially true for permethrin, a second-generation pyrethroid. Permethrin is available in several formulations and is particularly prominent in over-the-counter products, for which efficacy data are difficult to find. Among the formulations which have been extensively evaluated, spot-on formulations include a 65%-permethrin spot-on [35-37] (Defend Exspot – treatment for dogs – Schering-Plough Animal Health), combination products e.g. imidacloprid10%/permethrin 50% [14, 15] (K9 Advantix® – Bayer) and pyriproxyfen 0.3%/permethrin 40% (Duowin® Contact – Virbac). Sprays containing 2% permethrin (Defendog® – Virbac) or combination products such as pyriproxyfen 0.02%/permethrin 1.9% (Duowin® – Virbac) are also available. Efficacy against fleas was assessed in several trials. After one application, under controlled conditions, adulticidal efficacy of the imidacloprid 10%/permethrin 50% product was 99.4% (day 1), 95.7% (day 29) and 90.4% (day 36) [15]. The same formulation was assessed in a field trial at 23 centres in Germany, France and Italy on 229 dogs treated once. 134 other dogs were treated once with a topical 10% fipronil formulation. The immediate (day 2) efficacy against fleas of the imidacloprid permethrin combination vs. the control product was 98.3% vs. 97.0%. Residual efficacy (day 28) of the two products was 92.5% vs. 93.5% [14].

**Metaflumizone**

Metaflumizone (Promeris®, Promeris®Duo – Fort Dodge) is derived from pyrazoline and acts by binding the voltage-dependent sodium channels in insects. Studies in controlled environment (experimental infestations, comb-counts 48h after treatment and re-infestations) showed over 90%-efficacy for 6 weeks in dogs [38] and 7 weeks in cats [39]. Speed of kill was evaluated in adult cats and compared with a product containing a combination of fipronil-(S) and methoprene. It was found to be slower [40]. A European multicentric study was performed on 170 dogs with flea infestation, randomly allocated to one of two treatments, metaflumizone plus amitraz (minimum dosage of 20 plus 20mg/kg) or fipronil (at the recommended label rate). Both treatments resulted in consistent (>89%) reductions in flea numbers relative to baseline counts, throughout the study (8 weeks), although fipronil resulted in numerically higher reductions on each count day [41].

**Spinosad**

Spinosad is an aerobic fermentation product of the soil bacterium, Saccharopolyspora spinosa. Spinosad kills insects through activation of the acetylcholine nervous system through nicotinic receptors. The mode of action is unique and incompletely understood. It is available in the United States as an chewable tablet (Comfortis® – Lilly). Its efficacy against fleas
appears excellent (98-100%) [42, 43]. A recent controlled study showed that when administered to infested dogs, efficacy was 81%, four hours post-treatment. When treated animals were re-infested, efficacy was over 96% for 14 days, four hours after infestation [44].

**Juvenile hormone analogues (JHAs)**

The pharmacological properties of juvenile hormone analogues are characterised by mimicking the juvenile hormones of insects resulting in interference with metamorphosis and reproduction. Prevention of larval development breaks the flea life cycle. Due to specificity of juvenile hormone for insects, pyriproxyfen has virtually no effects on mammals. Two products, methoprene and pyriproxyfen, are used for flea control, either administered to the animal or applied in the environment. They are usually combined with an adulticide: fipronil (Frontline® Combo/Frontline® Plus – Merial) [45] or permethrin (Duowin®, Duowin®Contact – Virbac). A spot-on containing 1% pyriproxyfen only (Fleegard® - Bayer) [46] and a commercial diet (Virbac Vet Complex® dermatology – Virbac) containing 50 mg/kg are also available in several countries.

**Insect developmental inhibitors (IDIs)**

Lufenuron (Program® - Novartis) is a systemic IDI which interferes with chitin synthesis, polymerisation and deposition [47]. Lufenuron has no effect on adult fleas. Excreted in flea faeces, it prevents normal pupation of larvae feeding on those flea faeces. Numerous studies have shown its efficacy either administered orally to dogs or cats or injected to cats [18, 28, 48-50]

**Recommendations**

**As yet, the ideal product does not exist**

Flea avoidance is certainly the goal for a dog or cat with FAD. This is difficult and takes time. Symptomatic, antipruritic therapy (beyond the scope of this article) is often necessary. Furthermore, there are so many opportunities for a dog to pick up fleas (e.g. environment, neighbourhood and occasional visiting animal) that even if flea control is considered optimal, it may still fail. Allergen-specific immunotherapy has, to date, not been helpful.

The ideal product to protect an animal with FAD against fleas would be one with repellent action, i.e. a product which ideally, would prevent fleas (mainly newly-emerged adults but also fleas coming from infested animals) from jumping on, or at least disturbing any fleas that did arrive in the coat so that they would leave immediately without biting (flushing effect). Unfortunately, although such products are effective against some insects (e.g. mosquitoes), they are not very helpful in flea control.

One should remember that a newly-emerged flea will start feeding within a few minutes of its arrival on the host. The first blood meal lasts from 10 minutes (males) to 25 minutes (females) [3]. It is therefore, not surprising that none of the aforementioned products is able to kill fleas before the fleas start to bite. However, some of them (particularly pyrethroids, but also nitempyram and spinosad) can certainly shorten the blood meal duration thereby reducing the amount of saliva injected.

A female flea starts laying eggs within 24-36 hours and then continues to do so for the rest of its life. Consequently, to prevent additional environmental contamination, a product which becomes effective in under 24 hours should be recommended.

**Adulticidal products on the animal with FAD**

Given what has already been said about the testing and evaluation of antiparasitic substances, and also the effects of over-grooming, excessive bathing, and skin inflammation on reducing product efficacy, it might be wise either to apply a product more frequently (for example, every 2-3 weeks) than recommended by the manufacturer or, better still, alternate every fortnight, between two different products each with a different mode of action.

The efficacy of insecticidal products is dose-dependent. The dose itself is time-dependent, varying according to whether the product is applied all over the body surface or to a more restricted area. Systemic products have the advantage of not being altered by any skin change/action. Similarly, applying a product all over the body (e.g. spraying in dogs), should, assuming the correct dose is given, ensure rapid and homogenous covering of the body surface with adequate amount of product.

**Treatment of in-contact-animals**

All must be treated, including cats. Their treatment regimen does not have to be as strict as that of the pet with FAD. A single adulticidal product (instead of possibly two on the animal with FAD), applied according to the manufacturer’s recommendations (instead of every fortnight) should be suggested. Should the animal with FAD be treated with a systemic (or possibly topical) IGR such as lufenuron (or methoprene/pyriproxyfen), all in-contact animals should also be treated.

**Targeting the different steps of the life cycle: integrated control**

An insect growth regulator (IGR) - JHA or an IDI - should be combined with an adulticide(s), either on the animal or in the environment. Prior to application of flea control products in the environment, hygienic measures should be recommended, bearing in mind the relative lack of efficacy of vacuuming against larvae. Prior steam cleaning should be suggested.

When premises are too large, or when young children are at high risk of coming in contact with the products (particularly pyrethroids) whilst playing on carpets, the IGR should be administered directly to the animal, preferably systemically.

**Customising flea control**

Factors which may influence failure in a flea control programme may be product-related or animal/owner-related. Client compliance, short-term and long-term, is essential in FAD cases. Therefore, any control plan has to be practical for the owner and must be adapted to individual circumstances. Compliance, ability, health, financial resources, presence of young children, degree of pet and owner contact must all be taken into consideration.
Conclusion

Despite the availability of safe, effective products, treating FAD remains a challenge. This challenge should be more readily overcome once both practitioner and owner(s) are entirely convinced of the diagnosis. Appropriate knowledge of the flea life cycle and flea-related biology, an understanding of the mode of action of flea control products, and motivation are all required. An integrated approach to treatment should be adopted, involving all the players in the flea life cycle - the FAD patient, all in-contact pets, and the environment. Each case must be customised, with effective flea control products used in combination with cleaning measures such as steaming, vacuuming and regular grooming.

References