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Comparative speed of efficacy against *Ctenocephalides felis* of two oral treatments for dogs containing either afoxolaner or fluralaner

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ABSTRACT

A study was designed to compare the efficacy of NexGard® and Bravecto™, 2 recently introduced oral ectoparasiticides containing isoxazolines, against fleas (*Ctenocephalides felis*) on dogs. Twenty-four healthy dogs, weighing 9.2 kg to 28.6 kg, were included in this parallel group design, randomized, and controlled efficacy study. On Day −1, the 24 dogs were allocated to 3 study groups: untreated control; Nexgard® treated and Bravecto™ treated. The treatments were administered on Days 0, 28 and 56 for Nexgard® (labelled for monthly administration), and once on Day 0 for Bravecto™ (labelled for a 12 week use). Flea infestations were performed weekly with 100 adult unfed *C. felis* on each dog from Days 42 to 84. Fleas were counted and re-applied at 6 and 12 h post-infestation and removed and counted 24 h post-infestation. The arithmetic mean flea count for the untreated group ranged from 62.9 to 77.6 at 24 h post-infestation, indicating vigorous flea challenges on all assessment days. Both the Nexgard® and Bravecto™ treated groups had statistically significantly ($p < 0.05$) less fleas compared to the untreated group on all assessment time points and days. Significantly fewer fleas were recorded for NexGard® treated dogs compared to Bravecto™ treated dogs at 6 h post-infestation on Day 56, 63, 70, 77 and 84 and at 12 h post-infestation on Days 70 and 84. No statistically significant ($p < 0.05$) differences were recorded between the treated groups at 24 h post-infestation. Efficacies recorded 6 h post-infestation for Nexgard® ranged from 62.8% (Day 49) to 97.3% (Day 56), and efficacies ranged from 94.1% (Day 49) to 100% (Days 42, 56, 70 and 84) at 12 h post-infestation. Efficacies recorded for Bravecto™ ranged from 45.1% (Day 84) to 97.8% (Day 42) at 6 h post-infestation, and from 64.7% (Day 84) to 100% (Days 42 and 56) at 12 h post-infestation. Efficacies observed at 24 h were 100% for both products during the study except 99.6% on Day 84 for Bravecto™.

1. Introduction

Fleas represent one of the most prevalent parasites in domestic carnivores (Beugnet et al., 2014a,b). In addition to causing discomfort to pets and their owners, *C. felis* is primarily responsible for flea bite allergy dermatitis in both dogs and cats (Dryden and Rust, 1984). Cat fleas are also vectors of several pathogens including *Dipylidium caninum*, *Rickettsia felis*, and *Bartonella henselae* (Otranto et al., 2009a, 2009b).

Although the use of insecticides such as fipronil, imidacloprid, selamectin, and spinosad have revolutionized

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flea control in the recent years, treatment and prevention of cat flea infestations remain a major concern for pet owners and veterinarians (Beugnet and Franc, 2012; Halos et al., 2014). Licensed products must reach standards of efficacy determined by pharmaceutical regulatory authorities worldwide (e.g. European Medicine Agency (EMA) in Europe, Environmental Protection Agency (EPA) or Food and Drug Agency (FDA) in the USA) (EMEA, 2000; Marchiondo et al., 2013). To meet EMA guidelines, the efficacy of a drug against fleas must reach at least 95%, 48 h post infestation for a given time-point in several controlled standard studies.

Several criteria are judged important for both veterinarians and pet owners: the ease of treatment, the duration of efficacy, and the speed of kill (Beugnet and Franc, 2012; Halos et al., 2014; Otranto and Wall, 2008). The convenience of administration is a key factor for treatment compliance. In that aspect, topical spot-on formulations represented a major advance in the 1990s. More recently, chewable oral flea or flea and tick control formulations have been developed. Depending on the palatability, the dogs may spontaneously consume the chewable tablet which contains the insecticide-acaricide. Both afoxolaner and fluralaner are new insecticide-acaricide molecules from the isoxazoline family that act on the insect γ-aminobutyric acid receptor (GABA) and glutamate receptors, inhibiting GABA and glutamate-regulated uptake of chloride ions resulting in excess neuronal stimulation and death of the arthropod (Gassel et al., 2014; Lahm et al., 2013; Shoop et al., 2014). Afoxolaner is the active ingredient of Nexgard® (Otranto, 2014), and fluralaner is the active ingredient of Bravecto™ (Rohdich et al., 2014). The two formulations are highly palatable to enhance compliance of treatments administered by dog owners. Due to their pharmacokinetic properties and the minimum dose administered, 2.5 mg/kg of afoxolaner and 25 mg/kg of fluralaner, respectively, they provide long-lasting insecticidal and acaricidal activity against fleas and ticks (Letendre et al., 2014; Kilp et al., 2014). Nexgard® administered to dogs has been shown to kill 100% of fleas within 24 h after infestation for 5 weeks (Hunter et al., 2014), and Bravecto™ has been demonstrated to kill 100% of fleas within 48 h after infestation for 12 weeks, according to the U.S. product label (Bravecto prescribing information. Summit, NJ, Merck Animal Health, 2014).

Speed of kill is also an important criterion for assessing a flea control product, because the more quickly fleas are killed the less likely a pet owner is to observe them on the pet. Speed of kill also influences flea egg production, and faster speed of kill therefore results in less flea egg contamination of the environment (Beugnet et al., 2014a,b; Hunter et al., 2014; Williams et al., 2014). Both NexGard® and Bravecto™ have demonstrated a flea efficacy above the threshold of 95% starting as early as 4–8 h after flea challenges (Beugnet et al., 2014a,b; Hunter et al., 2014). Based on the published data on the duration of efficacy, as well as the potential speed of kill, the aim of this study was to compare the speed of kill against fleas between one Bravecto™ administration and 3 successive 28 day administrations of NexGard®, according to their respective labelling in Europe (Beugnet et al., 2014a,b; Hunter et al., 2014; Rohdich et al., 2014).

2. Materials and methods

2.1. Study design

The study was a parallel group design, randomized, single centre, blinded, controlled, efficacy study. In order to prevent any bias, the treatments were not administered to dogs by an individual involved in performing the post-administration assessments and observations. The groups were coded to blind the staff performing post-administration observations and assessments. The study was conducted on three groups of 8 dogs each. The study was authorized by both Merial and ClinVet ethical committees, and was conducted in respect of the Good Clinical Practices as described in International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline GL9 (EMEA, 2000). Group 1 dogs remained untreated while group 2 dogs were treated orally with NexGard® and group 3 dogs with Bravecto™.

The design of the study is shown in Table 1. The study followed a randomized block design. The 24 dogs included were ranked within sex in descending order of individual pre-administration flea counts and subsequently blocked into eight replicates of three dogs each. Within blocks, dogs were randomly allocated to three coded groups. The coded groups were randomly assigned to the treatments by a non-blinded person external from the study staff.

2.2. Animals

In order to assess the individual susceptibility to flea bites, 27 dogs were originally challenged with fleas and the 3 dogs with the lowest flea infestations were excluded. The 24 included dogs were males and females of mixed breeds, older than 6 months, with no restriction hair length, and weighing between 9.2 and 28.6 kg. They were

Table 1
Study design.

Acclimatation	Flea infestations	Ranking and allocation to the 3 groups	Treatments	Assessments at 6 and 12 h – in situ flea counts	Assessments at 24 h – flea counts and removal
Days −14 to −1	Days −7, 42, 49, 56, 63, 70, 77 and 84	Day −2 (±1 day)	NexGard®: Day 0, 28 and 56 (Group 2) Bravecto™: Day 0 (Group 3)	Days 42,49, 56, 63, 70, 77 and 84	Days −5, 43, 50, 57, 64, 71, 78 and 85