

Comparison of Preference Demonstrated by Dogs When Offered Two Commercially Available Oral Ectoparasiticide Products Containing either Afoxolaner (NexGard®/Frontpro®) or Lotilaner (Credelio®/AdTab™)

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Abstract

Fleas and ticks infest dogs worldwide and represent major veterinary and public health issues. Their control requires repeated use of ectoparasiticide products during periods of exposure. Lack of compliance to recommended treatment regimen is a prime reason for lack of efficacy, especially when treatments need to be administered repeatedly. Isoxazoline formulations are commercially available in several palatable oral products for dogs, providing convenient and efficient solutions to control fleas, ticks and other ectoparasites. Repeated oral administrations need to be an easy experience for both the dog and its owner, to maintain compliance. It is therefore valuable for dog owners and veterinarians to know whether some products are preferred by dogs in comparison to others. The present study investigated dogs' preference between an afoxolaner chewable tablet (NexGard®/Frontpro®, Boehringer Ingelheim) and a lotilaner chewable tablet (Credelio®/AdTab™, Elanco). Once a day, for four consecutive days, one hundred dogs were offered the opportunity to smell both products and then choose and eat one product. This allowed a calculation of consumption rates (number of tablets voluntarily consumed) and preference rates (number of dogs expressing a preference for one product versus the other). Over the four days, 354 tablets were voluntarily consumed (88.5%). A total amount of 221 (62.4%) NexGard tablets and 133 (37.6%) Credelio tablets were consumed, making a 1.67 to 1 overall consumption ratio in favor of

NexGard ($p < 0.05$). Among the 69 dogs showing a preference over the four-day test period, 53 dogs (76.8%) preferred NexGard, while 16 dogs (23.2%) preferred Credelio ($p < 0.0001$), resulting in a preference ratio of 3.31 to 1 for the afoxolaner formulation versus the lotilaner formulation. This study showed that when given a daily choice for four consecutive days to 100 dogs, there was an overall preference for consuming the afoxolaner chewable formulation versus the lotilaner formulation.

Keywords

Afoxolaner, Lotilaner, Consumption, Preference, Ectoparasiticide

1. Introduction

Ectoparasite infestations affect canine and feline populations worldwide and represent major veterinary and public health concerns through their direct pathogenic effects on animals and their role as vectors of numerous pathogens, including zoonotic agents [1]-[3]. Consequently, regular preventive and, when necessary, curative treatments of companion animals are necessary. Veterinarians and expert associations such as the European Scientific Counsel Companion Animal Parasites (ESCCAP) recommend permanent protection during exposure periods, continuous or seasonal for fleas and ticks in most parts of the world [4] [5]. Many registered veterinary products are available for treatment and prevention of fleas, and/or ticks but also for mites, lice and flying insects. For registration in Europe, veterinary products must consistently reach a defined threshold of efficacy, *i.e.* 95% reduction for fleas within 24 h of infestation and 90% reduction for ticks within 48h of infestation, during their claimed efficacy duration [6]. Nevertheless, non-compliance to treatment regimen is a recognized cause of lack of efficacy for ectoparasiticide drugs [7]-[10].

Over the last decade, isoxazolines, a class of ectoparasiticide compounds characterized by a high affinity and antagonism to ligand-gated chloride channels in GABA receptors of arthropods, and by systemic absorption and distribution in the treated companion animal patient, have appeared [11]. These drugs are available in oral, topical, and injectable forms, with efficacy durations for the oral forms of one to three months. A palatable and easy-to-administer oral isoxazoline product with a one-month duration of efficacy is an appropriate solution to maximize compliance and adapt the administration of the product to the dog's needs, during the flea and tick exposure periods. There are currently four ectoparasiticide isoxazoline formulations for dogs with these characteristics, *i.e.* NexGard/FrontPro® (afoxolaner), Credelio/AdTab® (lotilaner), Simparica® (sarolaner), and Bravecto® (fluralaner, available in 2 formulations providing either 1-month or 3-month duration of efficacy, without palatability claim, however with “well accepted” label description).

The Committee for Medicinal Products for Veterinary Use (CVMP) of the Eu-

ropean Medical Agency (EMA) has produced a Guideline on the demonstration of palatability of veterinary medicinal products [12]. To be considered palatable, an oral product must be voluntarily consumed by at least 80% of dogs. Palatability is an important criterion of choice for an oral product administered repeatedly. It is nevertheless subjective, as granted on the basis of group acceptance of a single product, while individual dogs may react differently following repeated administrations during long periods of time. It is thus helpful for the veterinarian and the dog owner to be informed about any preference dogs may have for any of these products. Paired preference tests are appropriate to provide such answers [13]. A preference test follows a two-option free choice testing design, addressing the question of the preference of one product against the other, while a palatability test is based on acceptance of a single product.

The study presented in this manuscript tested preference between NexGard® and Credelio®. In the EU, NexGard is available as a prescription only medicine (POM) under this name, and as an “over the counter” drug (OTC) under the name of Frontpro®. Similarly, Credelio, a POM product, is available as an OTC drug under the name of AdTab®. For both products, the POM and OTC forms are identical formulations.

2. Materials and Methods

Animals were managed similarly and with due regards for their well-being. The study design was reviewed and approved by the sponsor’s (Boehringer Ingelheim Animal Health) and local (BerTek, Inc.) institutional animal care and use committees. The study design and trial facility met the USDA-APHIS animal welfare requirements, and the dogs were housed in individual enclosures of a size in accordance with the Animal Welfare Act.

2.1. Animal Characteristics and Husbandry

One hundred healthy cross breed (54) or beagle (46) dogs, 58 intact males, 41 females and one spayed female, weighing between 10 and 16 kg and aged 11 months to 9 years old were included in the study. The dogs belonged to the BerTek Inc. colony, originally sourced from Class-A breeders Freeman Farms and Marshall BioResources. To be included in the study, the dogs had to comply with the conditions and precautions of use described in the Summary of Product Characteristics of NexGard [14] and Credelio [15]. The dogs had not been exposed to any ectoparasiticide product for at least 75 days prior to the start of this study.

Dogs were acclimated to study conditions for seven days before study start. Commercial dry canine food (Loyall, Adult Maintenance Formula, Nutrena) was provided once a day in an amount meeting dogs’ individual nutritional requirements and fresh potable tap water was provided *ad libitum*.

2.2. Test Products

NexGard chewable tablet for dogs 2.5 to 5 kg (11.3 mg afoxolaner) and Credelio

chewable tablet for dogs 2.5 - 5.5 kg (112.5 mg lotilaner) were offered to all dogs during the study. The dogs received the smallest similarly sized commercially available form of each product, without consideration of their bodyweight, as the objective of the study was the preference testing rather than a pharmacological activity testing. This also allowed minimizing the dose of medication administered to each dog and making the two products close in size. The decision to administer the smallest available dose size to dogs whose body weights were approximately two to three times greater than the product's recommended weight range ensured that the 4-day dosing regimen remained well within established safety margins. Health observations and adverse event monitoring were conducted daily, and no adverse events were recorded.

2.3. Preference Testing Procedures

The testing procedure was performed once a day for four consecutive days. The entire tablet offering was performed by the same operator for all dogs and on each study day.

Each tablet offering was performed at least 4 hours after the daily feeding procedure.

On the first day Credelio was chosen by flip of coin to be offered in the left hand, thus NexGard was offered in the right hand. The hands holding the products were reversed each day (to ensure that any hand-preference was negated), for four consecutive days. Blinding of the operator was not possible, as the operator was required each time to verify that each product was applied to the correct assigned hand.

Immediately before opening of each dog cage, the operator took one tablet of each product in the appropriate latex-gloved hand. The products were held in the fingertips, positioned at the level of the dog's head, approximately 30 cm apart and equidistant from the dog, allowing the dog to smell each product. Then the products were moved into the palms, and both hands were opened, allowing the dog to take a product from one hand or the other. After the dog selected one of the products, the opposite hand was closed, and both hands were placed behind the operator's back. If the dog took neither of the products within one minute, no consumption was recorded. The dog was then observed for consumption of the chosen product. If the product was expelled from the mouth, the dog was allowed approximately 30 seconds to take the product back into its mouth and consume it. If, after this time period elapsed, the dog did not take this product back into its mouth, the dropped product was picked back up with the appropriate hand, and both products were offered again, in the same fashion as the previous offering. If, after one minute, the dog chose neither product, no consumption was recorded for that dog, for that day. The identity of the product (or none) that was ultimately consumed by each dog was recorded.

The data collected on each day of dosing recorded were, "First Product Taken", "Product Dropped", and "Product Finally consumed". The primary endpoint was

the final voluntary consumption.

2.4. Statistical Methods

All analyses and calculations were performed using SAS Version 9.4. Statistical significance was declared at a two-sided p-value of 0.05.

To determine the overall preference for NexGard, Credelio, or neither, the number of times each product was consumed was compared for each dog. If one product was consumed more frequently than the other (*i.e.* 4/0, 3/0, 2/0, 1/0, 3/1, 2/1), the dog was defined as preferring that product. Where the number of items consumed was tied (0/0, 1/1, 2/2), the dog's preference was defined as "none."

The proportion of dogs consuming NexGard on each day and the proportion of dogs preferring NexGard over the four daily offerings was compared to 50% (equal numbers of dogs preferring each product) ignoring dogs that consumed neither product (daily) or that preferred neither product (overall), using a chi squared test.

3. Results

Consumption of chewable tablets and preferences are summarized in **Table 1**.

Table 1. Summary of consumption data and preference.

	Consumption (chewable tablets)			p-value*
	Afoxolaner	Lotilaner	None	
Day 0	52	35	13	0.0316
Day 1	55	32	13	0.053
Day 2	50	37	13	0.0793
Day 3	64	29	7	<0.0001
Total	221	133	46	<0.05
Overall preference (dogs)				
	53 (76.8%)	16 (23.2%)	31	<0.0001

*chi squared test between the afoxolaner and lotilaner groups.

Over the four days of the study, 354 chewable tablets were consumed (88.5%) and there was no consumption in 46 instances (11.5%). When consuming a product, most dogs clearly accepted their first-choice daily offering (consumption of a dropped product following a second offering or consumption of the other product following a drop of a first-choice product rarely occurred). A total amount of 221 (62.4%) afoxolaner chews and 133 (37.6%) lotilaner chews were consumed, making a 1.67 to 1 overall consumption ratio in favor of afoxolaner over lotilaner. On Days 0 and 3, significantly ($p < 0.05$) more dogs consumed afoxolaner than lotilaner compared to equal consumption (50%), with afoxolaner consumption at 60%, 63%, 57% and 69% of the dogs that consumed a product on Days 0, 1, 2 and

3, respectively (**Table 1**).

Among the 69 (69%) dogs showing a preference over the entire test period, 53 dogs (76.8%) preferred NexGard, while 16 dogs (23.2%) preferred Credelio ($p < 0.0001$).

No adverse reactions were reported in any dog, at any time, during the trial.

4. Discussion and Conclusion

This study showed that when given a daily choice for four consecutive days to 100 dogs, there was an overall preference for consuming the afoxolaner chewable formulation versus the lotilaner formulation.

Table 2 represents the composition of both formulations. The NexGard formulation is engineered as a flavored “soft chew”. Its main non-active ingredients are corn starch, soy protein fines and other constituents such as glycerol and triglycerides giving a soft treat texture, and a braised artificial additive as flavoring agent [14]. Smaller and denser, Credelio has a more classic tablet-like matrix with compression chemical agents, and a beef additive flavoring agent [15]. These different chemical and physical characteristics may explain the preferences observed in this study for NexGard. Meat based flavors and complex mixtures of flavors seem to be natural preferences in dogs [16]. The study design did not permit isolation of the individual effects of the active ingredient, flavor, texture, tablet size, or excipient matrix, representing a limitation of the study.

Table 2. Qualitative composition (main ingredients) in the afoxolaner and lotilaner chewable tablets [14] [15].

Tradenames (POM/OTC)	NexGard/Frontpro	Credelio/AdTab
Active ingredient	Afoxolaner	Lotilaner
Excipients and other non-active constituents	Maiz starch	Cellulose, powdered
	Soy protein fines	Lactose monohydrate
	Beef braised flavouring	Silicified microcrystalline cellulose
	Povidone (E1201)	Meat dry flavour
	Macrogol 400	Crospovidone
	Macrogol 4000	Povidone K30
	Macrogol 15 hydroxystearate	Sodium laurilsulfate
	Glycerol (E422)	Silica, colloidal anhydrous
	Triglycerides, medium chain	Magnesium stearate

POM = “Prescription-Only Medicine” status; OTC = “Over The Counter” status.

NexGard® has already been tested for preference against Simparica® and

Bravecto® and was demonstrated each time the preferred product [17] [18]. NexGard Spectra®, an endectoparasiticide oral tablet combining afoxolaner and milbemycin oxime, also formulated in a soft chew almost identically to NexGard, was demonstrated a preferred choice versus Simparica Trio™, a palatable chewable tablet for dogs combining sarolaner, moxidectin and pyrantel embonate, and versus Credelio® Plus, a palatable chewable tablet for dogs combining lotilaner and milbemycin oxime [19] [20]. These different studies sustain the hypothesis that against other isoxazoline oral formulations, the chewable matrix of afoxolaner oral formulations are usually the preferred option.

Repeated administration needs to be an easy experience for both the dog and its owner to maximize chances of lasting compliance. Considering the importance of the treatment and control of ectoparasiticides in dogs, both for veterinary and public health reasons, and the necessity of repeated administration of ectoparasiticides during the dog's life, the oral preference of the afoxolaner soft chew is a valuable information for the veterinarian and the dog owner.

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Availability of Data and Materials

All relevant data are provided within the paper.

Ethics Approval and Consent to Participate

The study was approved by BerTek Inc. Animal Care and Use Committees (IACUC) with the concurrence of Boehringer Ingelheim.

Consent for Publication

All authors have reviewed this document and consent to publish the data.

Author Contributions

William R. Everett: study protocol, investigation, general supervision. Eric Tielemans: Manuscript drafting.

Conflicts of Interest

The work reported herein was funded by Boehringer Ingelheim. Eric Tielemans is a current employee of Boehringer Ingelheim, and was not involved in the statistical analysis or results interpretation. Other than that, the authors declare no conflict of interest. This document is provided for scientific purposes only. Any reference to a brand or trademark herein is for information purposes only and is not intended for any commercial purposes or to dilute the rights of the respective owners of the brand(s) or trademark(s).

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