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Preference in Dogs of Two Oral Endectoparasiticide Formulations: NexGard Spectra® (Afoxolaner and Milbemycin Oxime) and Credelio® Plus (Lotilaner and Milbemycin Oxime)

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Abstract

Fleas and ticks are major ectoparasites of dogs globally. Their control is based on regular treatments with ectoparasiticides, which represent the most important part of veterinary drugs worth around 3 billion Euros per year. In many parts of the world, dogs are also at risk of infection by endoparasites like heartworm, eyeworm, and lungworm. In these areas, endectoparasiticide formulations are used to prevent the risk of ecto- and endoparasite infections. Since 2014, oral formulations of insecticidal-acaricidal drugs have been launched, followed by endectoparasiticide formulations. These oral formulations facilitate the treatment by the owners and are now the market leaders. Intense work has been done during their development to enhance their palatability through their consistence (hard to soft) and their flavors. Palatable oral formulations facilitate the dog-owner relationship and help ensuring compliance. The most recent palatable formulations include isoxazoline as the ecto-parasiticide molecule. They also include anthelmintics (milbemycin oxime or moxidectin + pyrantel) to provide control of parasitic nematodes. Being very similar in terms of spectrum of activity, any differences in palatability may be a key differentiating factor for the owners. The present study was conducted to verify if dogs exhibited a preference between two endectoparasiticide oral formulations, NexGard Spectra® (afoxolaner and milbemycin oxime) and Credelio® Plus (lo-

tilaner and milbemycin oxime). For four consecutive days, 100 dogs were offered the choice between both products and consumption was recorded. If one product was more consumed than the other, it was defined as the preferred product. A total of 375 chewable tablets were consumed over the four days, with a significantly higher consumption ($p < 0.0001$) for NexGard Spectra® (272 chews, 72.5%) compared to Credelio® Plus (103 chews, 27.5%). Seventy-six dogs showed a preference for a product amongst whom 68 preferred NexGard Spectra® (89.5%) and 8 preferred Credelio® Plus (10.5%), resulting in a preference ratio of 8.5 to 1 for NexGard Spectra® ($p < 0.0001$).

Keywords

Preference, Chewable Tablet, NexGard Spectra®, Credelio® Plus, Palatability

1. Introduction

Pet owner compliance is essential for the success of veterinary healthcare strategies and treatments. Endectoparasiticide medicines are used in dogs to control infestation against major ectoparasites, *i.e.*, fleas, ticks and mites, and major endoparasites, *i.e.*, heartworm, roundworms, hookworms and whipworms [1]. Antiparasitic drugs represent the largest market in animal health, *i.e.*, 7.5 billion Euros, around 4.6 billion Euros for companion animals [1]. Guidelines prepared by veterinary parasitologists about the use of antiparasitic drugs in dogs and cats are available for both veterinarians and pet owners (https://www.esccap.org/, https://www.troccap.com/, https://capcvet.org/). Since 2014, the antiparasitic drug market for dogs has moved from spot-on topical formulations to oral formulations which are now leading the market. Oral formulations have been developed to ease the administration and have become possible with the arrival of a new class of systemic insecticides-acaricides. The most recent palatable formulations include an isoxazoline as the ectoparasiticide molecule. In many regions of the world, dogs are not only at risk of being infested by fleas and ticks, but also by internal nematodes such as the heartworm (*Dirofilaria immitis)*, lungworm (*Angiostrongylus vasorum*), eyeworm (*Thelazia callipaeda*) and gastro-intestinal nematodes (roundworms, hookworms, whipworms), thus the most recent combinations are endectoparasiticides (*i.e.*, NexGard Spectra®, Simparica Trio™, Credelio® Plus) [1] [2]. In these three oral formulations, isoxazolines (*i.e.*, afoxolaner, sarolaner, and lotilaner) provide activity against ectoparasites, and the anthelmintics (milbemycin oxime or moxidectin + pyrantel) provide control of parasitic nematodes. Being very similar in terms of spectrum of activity, the difference in palatability may be a key differentiating factor for the owners. Pet owners may encounter difficulties giving oral medications to their dogs. In some cases, they have to manually place the tablet at the back of the tongue and force the dog to swallow it, or hide the tablets in food, or crush and mix it in food or dissolve it in

water, etc. Palatable formulations help to ensure compliance and facilitate the dog-owner relationship [3] [4] [5]. Palatability is related to the consistence of the tablet, from hard to soft (so called "chew"), and the taste based on added flavoring agents. The complete formulations remain secret except for active and major ingredients and types of flavors.

To determine the palatability of oral veterinary products, the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medical Agency drafted a guideline (23 July 2021, EMA/CVMP/EWP/206024/2011-Rev.1) [6]. This guideline defines palatability as "the property of being acceptable to the mouth", "pleasant to the taste" or "acceptable to the taste".

Palatability tests are widely used in the pet food industry [7] [8]. The classical method is simply based on the acceptance of a given product, with a scoring of the easiness to administer. In a recent palatability field study, Credelio® Plus was administered to 355 dogs with 82.3% of these dogs taking the tablet without any difficulty (e.g. taking from an empty bowl or directly from the hand) and 17.7% of dogs needed it to be pilled in the mouth [9]. In the same study, NexGard Spectra® was administered to 151 dogs, and 80.8% of these dogs took the chew spontaneously (no significant difference with Credelio® Plus). In this study, no doses were refused.

An acceptance test is the first approach of palatability, but it does not allow direct comparison of palatability. For this purpose, a preference test, offering a choice to the animal is needed as a more sensitive method [4] [10] [11].

The objective of the present study was to determine the preference exhibited by dogs when simultaneously offered a choice between two endectoparasiticide oral formulations, NexGard Spectra® (launched in Europe in 2015) and Credelio® Plus, recently launched in Europe (*i.e.*, 2021).

2. Materials and Methods

The animals were managed similarly and with due regard for their well-being. Dogs were handled in compliance with Boehringer Ingelheim Institutional Animal Care and Use Committee (IACUC) approvals and the trial met USDAAPHIS animal welfare requirements. The design and condition of this study were performed in accordance with International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Guideline 9, entitled Good Clinical Practice.

2.1. Test Products

NexGard Spectra® (afoxolaner and milbemycin oxime) is formulated as a soft chewable tablet with artificial braised beef flavoring.

Credelio® Plus (lotilaner and milbemycin oxime) is formulated as a hard chewable tablet with a dry meat flavoring.

2.2. Animal and Housing

A total of 100 healthy beagle and crossbred dogs (53 males and 47 females), aged

between 1 and 8 year-old (mean 5 ≃ years, SD ± 2 years) and weighing between 8.0 and 15.8 kg (mean 11 kg, SD 2 kg) were included in the study. All dogs are part of a dog facility located in Arkansas, USA. Dogs were acclimatized to the study conditions for seven days. All dogs were observed daily, from acclimation start to the end of the study, for general health and adverse reactions. Dogs were housed individually with visual and auditory contact with conspecifics. Each morning, all dogs were fed an appropriate commercial ration according to body weight (Loyall, Adult Maintenance Formula, Nutrena). Fresh tap water was available to all dogs *ad libitum*. Dogs were maintained with a 12-hour-light/12-hour-dark cycle and temperature was maintained by the facility HVAC system within targeted conditions (22˚C). At the end of the study, all dogs returned to their colony.

2.3. Preference Procedures

For inclusion in the study, the willingness to accept product from an open hand was verified during the acclimation for each dog with a chicken treat, not to influence the dog's choice. Preference testing of the two products was conducted 4 hours after conclusion of daily feeding. The dogs were offered the smallest commercially available form of each product to minimize the dose of medication administrated during the study and to make the two compared products closer in size. NexGard Spectra® chewable tablets, 2 - 3.5 kg (9.375 mg of afoxolaner and 1.875 mg of milbemycin oxime) and Credelio® Plus chewable tablets, 1.4 - 2.8 kg (56.25 mg of lotilaner + 2.11 mg of milbemycin oxime) were offered simultaneously to all dogs, each day, during the four-day study. The same person performed the test with a given group of dogs on each study day.

For each dog, the product offered on the right hand on the first day was defined at random. Then for each dog, the hands offering the products were reversed the 3 following days (to avoid hand-preference of individual dogs).

At each offering, the products were held in the fingertips and dogs were first allowed to sniff them. Then, both hands were withdrawn and the products were moved to the palms. The opened hands were then positioned at the level of the dog's head approximately 30 cm apart and equidistant from the dog, for one minute, or until the dog took a chew from one hand.

If the dog did not take either product within one minute, "none" was recorded for that dog on that particular day.

When a product was taken from one hand, the other hand was closed around the remaining product and the operator placed both hands behind his back. The dog was observed for consumption of the chosen tablet for up to one minute. If a dog had dropped the chosen tablet and not taken it back within 30 seconds, the two products were presented a second time following the same procedure. No third attempts were made.

If one product was more consumed than the other over the 4 challenges, it was defined as the preferred product. Over the 4 days, the possible preference

combinations were 0/1, 0/2, 0/3, 0/4, 1/2, 1/3, and the non-preference combinations were 0/0, 1/1, 2/2.

2.4. Statistical Methods

The dog was the experimental unit. All statistical analyses were performed using R version 3.6.0 (R Core Team, 2019). Significance was defined at $p < 0.05$.

Product preference comparison

The frequency (in percentage) of dogs preferring NexGard Spectra® and the frequency (in percentage) of dogs preferring Credelio® Plus were compared to 50% (equal number of dogs preferring each product) ignoring dogs that did not prefer a product, using an exact binomial test.

Product consumption comparison

A Cochran-Mantel-Haenszel test was used to assess difference in the frequency (in percentage) of product consumption over the four study days per total experiment (NexGard Spectra®, Credelio® Plus and no consumption). The occurrence of NexGard Spectra® and Credelio® Plus consumption were then compared ignoring cases where dogs did not ingest a chew using a Wilcoxon signed-rank test with continuity correction, taking the pairing into account.

3. Results

No adverse events were recorded during the study.

Product preference

Table 1 shows the frequency (in percentage) of product preference for NexGard Spectra® or Credelio® Plus. Among the 76 dogs who preferred a formulation, 68 preferred NexGard Spectra® (89.5%) compared to 8 who preferred Credelio® Plus (10.5%), resulting in a preference ratio of 8.5 to 1 for NexGard Spectra® ($p = 5.63 \times 10^{-13}$).

Product consumption

Table 2 and Table 3 show the product consumption for NexGard Spectra® or Credelio® Plus. A total of 375 chewable tablets were consumed over four study days, with a significant higher consumption for NexGard Spectra® (272 chews,

Table 1. Frequency (in percentage) of product preference (NexGard Spectra® and Credelio® Plus) of dogs.

Dogs	NexGard Spectra®[1]	Credelio® Plus[1]	No preference[1]
All Dogs	68.0 [57.9; 77.0]	8.0 [3.5; 15.2]	24.0 [16.0; 33.6]
	(68/100)	(8/100)	(24/100)
Dogs with Preference	89.5 [80.3; 95.3][2]	10.5 [4.7; 19.7][3]	-
	(68/76)	(8/76)	-

[1]The results are presented as the frequency (in percentage) of product preference [95% confidence interval] and (product preference count/total dog number). [2]Exact binomial test: frequency of dogs with a preference for NexGard Spectra® was significantly higher than 50% (p-value = 5.63×10^{-13}). [3]Exact binomial test: frequency of dogs with a preference for Credelio® plus was significantly lower than 50% (p-value = 5.63×10^{-13}).

Table 2. Frequency (in percentage) consumptions per total experiment (NexGard Spectra®, Credelio® Plus, and none) of dogs stratified by day.

Day	NexGard Spectra®[1]	Credelio® Plus[1]	None[1]
Day 1	75.0 [65.3; 83.1] (75/100)	18.0 [11.0; 26.9] (18/100)	7.0 [2.9; 13.9] (7/100)
Day 2	56.0 [45.7; 65.9] (56/100)	33.0 [23.9; 43.1] (33/100)	11.0 [5.6; 18.8] (11/100)
Day 3	78.0 [68.6; 85.7] (78/100)	17.0 [10.2; 25.8] (17/100)	5.0 [1.6; 11.3] (5/100)
Day 4	63.0 [52.8; 72.4] (63/100)	35.0 [25.7; 45.2] (35/100)	2.0 [0.2; 7.0] (2/100)
Total over 4 Days	68.0 [63.2; 72.5] (272/400)	25.8 [21.5; 30.3] (103/400)	6.2 [4.1; 9.1] (25/400)

[1]The results are presented as the frequency (in percentage) of product consumptions [95% confidence interval] and (product consumption count/total experiment count). Analysing the data using the Cochran-Mantel-Haenszel test, the result is $M^2 = 24.642$, df = 6, p-value = 3.98×10^{-4}.

Table 3. Frequency (in percentage) of product consumptions per total consumption (NexGard Spectra® and Credelio® Plus) of dogs stratified by day.

Day	NexGard Spectra®[1]	Credelio® Plus[1]
Day 1	80.6 [71.1; 88.1] (75/93)	19.4 [11.9; 28.9] (18/93)
Day 2	62.9 [52.0; 72.9] (56/89)	37.1 [27.1; 48.0] (33/89)
Day 3	82.1 [72.9; 89.2] (78/95)	17.9 [10.8; 27.1] (17/95)
Day 4	64.3 [54.0; 73.7] (63/98)	35.7 [26.3; 46.0] (35/98)
Total over 4 Days	72.5 [67.7; 77.0] (272/375)	27.5 [23.0; 32.3] (103/375)

[1]The results are presented as the frequency (in percentage) of product consumptions [95% confidence interval] and (product consumption count/total consumption count). a) By treating the "None" as the missing data, it is not possible to perform the Cochran-Mantel-Haenszel test. b) Wilcoxon signed rank test with continuity correction. i) Comparing the consumption count between NexGard Spectra® and Credelio® Plus; ii) Repeated data on the same dogs for 4 days (non-independent) but the effects of time are not considered for this test; iii) p-value = 7.84×10^{-11}.

72.5%) compared to Credelio® Plus (103 chews, 27.5%), p = 7.84×10^{-11}.

Sex effect

Table 4 shows the results of preference by sex. No significant difference was observed for the dogs choosing NexGard Spectra® versus Credelio® Plus. But surprisingly, more males preferred Credelio® Plus than females compared to no choice (p = 0.037).

Table 4. Preference by sex.

Sex	NexGard Spectra®	Credelio® Plus	None	Total
Females	31	1	15	47
Males	37	7	9	53
Total	68	8	24	100
	Fisher's Exact Test NexGard Spectra versus Credelio Plus p-Value = 0.13			
	Fisher's Exact Test, NexGard Spectra versus No Preference p = 0.23	Fisher's Exact Test, Credelio Plus versus No Preference p = 0.037		

4. Discussion

This study demonstrated a significantly higher consumption ($p < 0.0001$) and preference ($p < 0.0001$) of NexGard Spectra® over Credelio® Plus in male and female dogs. In the present study, for the dogs that demonstrated a preference, 89.5% of them preferred NexGard Spectra® over Credelio® Plus. There was no sex effect in term of preference of NexGard Spectra® over Credelio® Plus, nevertheless a significantly higher number of males were counted within the group of dogs preferring Credelio® Plus (without particular explanation).

Companion animals tend to prefer meat-based flavors and complex mixtures of flavors [4]. Not only the flavor of a product influences its palatability, but also its texture, shape and size. The manufacturing process can also have an impact on palatability [4]. The two products studied have a meat taste with differences in flavoring agents and textures. NexGard® Spectra is softer, but in regards to the flavoring agents, they are not precisely listed in the product characteristics.

In the pet food industry, preference studies are typically performed with dogs in research centers or using pet dogs in the home environment. Even though research center dogs may not be considered representative of the "real-life" dogs, their environment is well controlled, and they are trained to perform palatability tests. The ultimate value of research centers is the repeatability of testing conditions, the control of environmental parameters, and the use of trained operators, thus limiting the variability compared to working directly with dog owners in homes, or vet nurses in veterinary clinics. To analyze this type of data, a minimum of 30 animals is necessary to ensure a secure statistical robustness [8].

The present study used 100 dogs and inclusion criteria which ensured heterogeneity of dogs and robustness of testing, *i.e.*, beagles and mix-breed dogs, 53 males and 47 females, with a large age panel (12 weeks to 7 years). The study was designed to minimize investigational bias. The test products were offered 4 hours after feeding to avoid any effect linked to food consumption. Offerings were done with gloved hands, and the products were hand-reversed each day to avoid any hand preference. The same person offered the products to each dog throughout the study, reducing operator variability. We could argue that a field study using owned dogs may allow a better reflect of the dog variability in sizes, breeds,

behaviors. Nevertheless, doing such a study in vet clinics would increase the bias by the number of involved people, the different environment, and the variable stress…these factors being controlled with experimental design.

The protocol used was similar to a previous preference study conducted with NexGard Spectra® and Simparica Trio™, a formulation including a liver pork flavor, which already gave significantly better results for NexGard Spectra® (where 94.7% of dogs preferred NexGard Spectra®) [12].

The NexGard Spectra® formulation is similar in terms of basic ingredients to that of NexGard®, except for the addition of milbemycin oxime, both of them contain the same base ingredients, and are formulated as a braised beef-flavored soft chew. Previous studies conducted with NexGard® demonstrated that dogs preferred this taste over other product: 93.1% dogs preferred NexGard® over Simparica™ (preference ratio: 13.5 to 1) [13], and 83% dogs preferred NexGard® over Bravecto® (preference ratio: 5 to 1) [14].

Preference tests are more sensitive than simple acceptance for the comparison of different formulations, but under field conditions, with a single offer, dogs could spontaneously accept a given formulation. As an example, in a recent field study, Credelio® Plus was proposed to 355 dogs with 82.3% of these dogs taking the tablet without any difficulty (e.g., taken from an empty bowl or directly from the hand) and 17.7% of dogs needing to be pilled in the mouth [9]. We can hypothesize that the better the palatability will be, as demonstrated in preference study, the easier it will be for an owner to successfully offer a chewable, but it doesn't mean that the overall acceptance is not good.

To ensure continued treatment and control, parasiticides should be administered at regular intervals, depending on parasite pressure, veterinary and manufacturer recommendations. Even though the majority of pet owners offer parasiticides, most of them do not administer antiparasitic drugs to their dog on a regular basis, resulting in a higher risk of parasitic infestations [15]; As an example, a recent European survey demonstrated that 93% of dogs belonged to the highest endoparasitic infection risk group, requiring monthly deworming. Yet, deworming frequencies were well below the recommendations to reduce zoonotic risk and improve pet health [16]. Pet owner compliance with veterinary recommendations is critical to ensure timely treatment and control of parasites in dogs. Importantly, anything that increases the ease of administration, such as improved palatability, also favors compliance and control of parasites.

5. Conclusion

This study demonstrated that when dogs were given the choice between the two commercially available endectoparasiticide formulations, NexGard Spectra® and Credelio® Plus, significantly more dogs preferred NexGard Spectra®.

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Conflicts of Interest

The authors are either employees or contractors of Boehringer Ingelheim Animal Health. NexGard Spectra is a trademark of Boehringer Ingelheim Animal Health. Credelio Plus is a registered trademark of Elanco.

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