

**Preference of Dogs between Two Oral Formulations of
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(Afoxolaner and Milbemycin Oxime) and Simparica Trio
TM (Sarolaner, Moxidectin and Pyrantel) Preference of
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Nadège Perier, Douglas Carithers, William Russel Everett, Sheila Gross, Phrutsamon Wongnak, et al..
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® (Afoxolaner and Milbemycin Oxime) and Simparica Trio TM (Sarolaner, Moxidectin and Pyrantel)
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(Afoxolaner and Milbemycin Oxime) and Simparica Trio TM. Open Journal of Veterinary Medicine,
2020, 10 (09), pp.155 - 163. 10.4236/ojvm.2020.109013 . hal-02952683

HAL Id: hal-02952683

<https://hal.inrae.fr/hal-02952683>

Submitted on 29 Sep 2020

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Preference of Dogs between Two Oral Formulations of Endectoparasiticides: NEXGARD SPECTRA® (Afoxolaner and Milbemycin Oxime) and Simparica Trio™ (Sarolaner, Moxidectin and Pyrantel)

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How to cite this paper: Perier, N., Carithers, D.S., Everett, W.R., Gross, S.J., Wongnak, P., Chalvet-Monfray, K. and Beugnet, F. (2020) Preference of Dogs between Two Oral Formulations of Endectoparasiticides: NEXGARD SPECTRA® (Afoxolaner and Milbemycin Oxime) and Simparica Trio™ (Sarolaner, Moxidectin and Pyrantel). *Open Journal of Veterinary Medicine*, 10, 155-163. <https://doi.org/10.4236/ojvm.2020.109013>

Received: August 24, 2020

Accepted: September 7, 2020

Published: September 10, 2020

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Abstract

Pet owner compliance is essential for the success of veterinary healthcare strategies. As some parasites are zoonotic, consistent parasite control is an integral part of the One-Health strategy. Highly palatable formulations help ensure compliance, as they offer a positive experience for the dog and the owner. This study was conducted to ascertain if dogs exhibited a preference between two commercially available oral formulations of broad-spectrum endectoparasiticides, NexGard Spectra (afoxolaner and milbemycin oxime) and Simparica Trio (sarolaner, moxidectin and pyrantel). For four consecutive days, 100 healthy dogs were offered both products and consumption was recorded. If one product was more consumed than the other, it was defined as the preferred product. No adverse event was recorded throughout the study. A total of 358 chewable tablets were consumed over four study days; 78.5% of dogs voluntarily consumed NexGard Spectra (281 chews), while 21.5% of dogs voluntarily consumed Simparica Trio (77 chews, $p < 0.01$). Among 75 dogs which demonstrated a preference for a product, significantly more dogs preferred NexGard Spectra (94.7%) compared to Simparica Trio (5.3%) ($p < 2.2 \times 10^{-16}$), resulting in a preference ratio of 17.75 to 1 for NexGard Spectra.

Keywords

Preference, Parasiticide, Palatability, Dog, Compliance

1. Introduction

Pet owner compliance, to preventive care and treatment recommendations, is essential for the success of veterinary healthcare strategies. It is not uncommon for pet owners to experience difficulty administering oral medications to their dog. In order to ensure the dog ingests the medication, they often have to force the dog to swallow it, and they have to hide the tablets in food, or crush the tablet and suspend it for administration in water, cheese, or another palatable form. This underscores the role that taste plays in ensuring compliance [1]. The development of palatable pharmaceutical formulations helps address compliance issues, with the desired outcome that the dog voluntarily consumes the medication. If the product is highly palatable, it will be readily accepted by the dog, essentially allowing a show of affection by pet owners of giving a treat to their dog [2]. In essence, preferred products are easy to give, and are considered as a treat by both the dog and the pet owner helping ensure a positive relationship between the dog and the owner [3].

To determine the palatability of veterinary medical products, the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medical Agency published a Guideline [4]. 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 [5] [6]. Classical methods are based on acceptance testing (one-option free choice testing format) and preference testing (two-option free choice testing format) [1] [7] [8]. The latter addresses the question “does the animal prefer one option over another” [1]. When there is an alternative, the animals can choose; therefore, preference tests are more sensitive than a simple acceptance test [1].

Ecto- and endoparasite infestations are common in dogs. Parasites can affect the dog’s overall condition, can cause skin lesions, affect the immune system, and transmit pathogens that may present zoonotic threats. The regular treatment and control of ecto- and endoparasites is essential for promoting well-being and maintaining healthy pets. NexGard Spectra (afoxolaner and milbemycin oxime), formulated in a soft chewable tablet with braised beef flavoring and Simparica Trio (sarolaner, moxidectin and pyrantel), formulated as a pork liver-flavored chewable tablet, are two monthly isoxazoline class based endectoparasiticides. NexGard Spectra is indicated for the treatment and/or prevention of flea, tick and mite infestations, for the control of a broad range of intestinal nematodes (roundworms, hookworms and whipworm), and for the prevention of heartworm, lungworm and eyeworm infections. Simparica Trio provides treatment of flea and tick infestations for one month in dogs, as well as roundworm and

hookworm infections, and prevention of heartworm and lungworm diseases. The objective of the study was to determine the preference exhibited by dogs when simultaneously offered a choice of both oral formulations.

2. Materials and Methods

All dogs 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 study met USDA-APHIS animal welfare requirements.

2.1. Animal and Housing

A total of 100 healthy purpose-bred dogs (65 males and 35 females, 38 Beagles and 62 cross-breed dogs) between 1 and 9 year-old (3.8 ± 1.8 year-old) and weighing between 8.0 and 18.1 kg (11.3 ± 2.1 kg) were included in the study. Dogs were acclimatized to the test facility for seven days. All dogs were observed daily, from acclimation start to the end of the study, for general health. Dogs were housed individually with visual and auditory contact with conspecifics. Each morning, all dogs were fed the appropriate ration according to body weight with commercial dry canine ration (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 (approximately 22°C). At the end of the study, all dogs returned to their colony.

2.2. Preference Procedures

During the acclimation period, dogs were qualified for inclusion in the study by assessing each dog's willingness to accept product from an open hand using a dog treat.

Preference testing of the two products was conducted at least 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 administered during the study and to have the products close in size. NexGard Spectra soft chewable tablets, 2 - 3.5 kg (9.375 mg of afoxolaner and 1.875 mg of milbemycin oxime), and Simparica Trio chewable tablets, 1.25 - 2.5 kg (3 mg of sarolaner, 0.06 mg of moxidectin and 12.5 mg of pyrantel), were both offered to all dogs, each day, in the four-day study. The same person performed the test with a given group of dogs on each study day.

Prior to study initiation in a random draw, NexGard Spectra was chosen to be offered in the left hand to each dog on the first day, and Simparica Trio was offered in the right hand. The hands offering the products were reversed each day (to avoid hand-preference of individual dogs).

At each offering, the products were held tightly in the fingertips and dogs were allowed to sniff them. Then, both hands were withdrawn and the products were moved to the palms of the hands. 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 tablet from one hand.

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

If a product was taken from one hand, the other hand was closed around the remaining product and the technician placed both hands behind his/her back. The dog was observed for consumption of the chosen tablet. If all or part of the product was expelled from the dog's mouth, the dog was allowed approximately half a minute to take the product back in its mouth and consume it. If, after this time period has elapsed, the dog had not taken the product, back into its mouth, the dropped product was retrieved with the appropriate hand, and both products were offered again, repeating the offering process a second time, as with the initial offering. If after one additional minute, neither product was taken by the dog, "none" was entered for that dog, for that day. The identity of the product that was ultimately consumed in its entirety or "none" was recorded for each dog on each day.

If one product was more consumed than the other, 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.

2.3. Statistical Methods

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

2.3.1. Product Preference Comparison

The occurrence of dogs preferring NexGard Spectra and the occurrence of dogs preferring Simparica Trio were compared to 50% (equal number of dogs preferring each product) ignoring dogs that preferred neither product, using an exact binomial test.

2.3.2. Product Consumption Comparison

A Cochran-Mantel-Haenszel test was used to assess any difference in the frequency (in percentage) of product consumption over the four study days per total experiment (NexGard Spectra, Simparica Trio and No consumption). The occurrence of NexGard Spectra consumed and the occurrence of Simparica Trio consumed were compared ignoring dogs that consumed neither product, using a Wilcoxon signed rank test with continuity correction and taking into account the pairing by dog.

3. Results

No adverse events were recorded during the study.

3.1. Product Preference

Table 1 shows the product preference for NexGard Spectra or Simparica Trio.

Table 1. NexGard Spectra and Simparica Trio product preference (%) by dogs.

| Dogs | NexGard Spectra ¹ | Simparica Trio ¹ | No preference ¹ |
|----------------------|--------------------------------|-----------------------------|-------------------------------|
| All dogs | 71.0 [61.1; 79.6] (71/100) | 4.0 [1.1; 9.9] (4/100) | 25.0 [16.9; 34.7] (25/100) |
| Dogs with preference | 94.7 [86.9; 98.5]** (71/75) | 5.3 [1.5; 13.1]** (4/75) | - - |

¹The results are presented as the frequency of product preference [95% confidence interval] and (product preference count/total dog number). ***The exact binomial test demonstrated that the frequency of dogs with a preference on NexGard Spectra is significantly higher than 50%, $p < 2.2 \times 10^{-16}$.

Among 75 dogs which demonstrated a preference for a product, 94.7% of dogs preferred NexGard Spectra (71 dogs), while 5.3% preferred Simparica Trio (4 dogs) ($p < 2.2 \times 10^{-16}$), resulting in a preference ratio of 17.75:1 for NexGard Spectra.

3.2. Product Consumption

Table 2 shows the product consumption for NexGard Spectra and Simparica Trio. Among 358 chewable tablets consumed over the four consecutive days, 78.5% of the dogs consumed NexGard Spectra (281 chews), while 21.5% consumed Simparica Trio (77 chews) ($p = 2.60 \times 10^{-13}$).

Table 2. NexGard Spectra and Simparica Trio product consumption (%) by dogs.

| | NexGard Spectra | Simparica Trio | No consumption |
|--|----------------------------------|---------------------------------|-------------------------------|
| Number of chews consumed on Day 1 | 58 | 24 | 18 |
| Number of chews consumed on Day 2 | 73 | 14 | 13 |
| Number of chews consumed on Day 3 | 67 | 27 | 6 |
| Number of chews consumed on Day 4 | 83 | 12 | 5 |
| % consumption or no consumption ¹ (Number of ingested or not ingested tablets) | 70.3 [65.5; 74.7]* (281/400) | 19.3 [15.5; 23.5]* (77/400) | 10.5 [7.7; 13.9]* (42/400) |
| % consumption ¹ (Number of ingested tablets) | 78.5 [73.9; 82.6]** (281/358) | 21.5 [17.4; 26.1]** (77/358) | - - |

¹The results are presented as the frequency of product consumptions [95% confidence interval] and (product consumption count/total count). *Analysing the data using the Cochran-Mantel-Haenszel test, the result is $M^2 = 29.681$, $df = 6$, $p = 4.52 \times 10^{-5}$. There is a significant difference among the variables (NexGard Spectra, Simparica Trio, and No consumption). **The Wilcoxon signed rank test with continuity correction demonstrated that significantly more dogs consumed NexGard Spectra than Simparica Trio over 4 days ($p = 2.60 \times 10^{-13}$).

4. Discussion

The objective of this study was to determine if dogs, when offered a choice, preferred NexGard Spectra or Simparica Trio.

In the present study, for the dogs that demonstrated a preference, 94.7% preferred NexGard Spectra over Simparica Trio ($p < 2.2 \times 10^{-16}$). NexGard

Spectra is a braised beef-flavored soft chewable tablet while Simparica Trio is a pork-liver-flavored chewable tablet. Companion animals tend to prefer meat-based flavors and complex mixtures of flavors [1] [9]. Not only the flavor of a product influences palatability, but also the components of the formulation, texture, shape and size. Prior experiences might also influence the dog's choice [10], however, little published data exists in this area.

In the pet food industry, preference studies are typically performed with experimental dogs in research centers or, using pet dogs, in their home environment. Even though some may not consider use of experimental dogs as representative of "real-life", the environment of research dogs is well controlled and dogs are trained to perform palatability tests on a daily basis. The ultimate value of research centers are the repeatability of testing conditions and the control of environmental parameters. It has been demonstrated that dogs can be influenced by their owners, leading to counterproductive choices [11]. When the same experiment was conducted with strangers and owners, there was no differential effect between them in directing the dog's choice [12]. Both owner and stranger could intentionally lead the dog to make the "wrong" choice (a smaller quantity of food or less palatable food). The use of trained technicians in research centers limits this variability compared to working directly with dog owners in homes, or even staff in veterinary clinics.

According to previous research, in order to analyze preference trends, a minimum of 30 animals is necessary to ensure the secure statistical robustness [6]. In our study, we included healthy Beagle and cross-breed dogs, 1 to 9 years old, to ensure the heterogeneity of the dogs tested, even though the dogs' weight did not surpass 18 kg. One-hundred dogs were included to ensure a solid study.

Numerous measures were taken to ensure this study design reduced any investigational bias. Products were offered at least 4 hours after feeding to avoid any effect linked to prior food consumption. The products were reversed each day to avoid any hand-preference. Both products were offered throughout the 4-day study to avoid a novelty effect. The same person offered the products to each dog throughout the study, reducing operator variability. Thus, the results reported in this paper are considered by the authors to be a fair assessment of the preference of dogs in a mixed population of dogs.

The excipients base of NexGard Spectra is close to that of NexGard®. Both products are formulated as a beef-flavored soft chewable tablet. Previous studies conducted with NexGard demonstrated that dogs preferred this beef-flavored soft chewable tablet over the other product tested: 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].

Parasites commonly affect dogs worldwide. As an example, flea infestations are considered the most common diagnosis in dermatological consultations in dogs in the UK [15]. While not as common as fleas, tick control is important as they are vectors of pathogens (e.g. *Babesia*, *Borrelia*, *Anaplasma*, *Ehrlichia*, etc.)

for dogs, and many of these pathogens are zoonotic [16] [17]. As with ectoparasites, intestinal parasites are common in dogs, especially in puppies, with some representing a zoonotic threat, such as *Toxocara canis* [18] [19] [20]. To ensure effective treatment and control, parasiticides should be administered at regular intervals, depending on local parasite pressure, veterinary and manufacturer recommendations. According to the ESCCAP guidelines [21] [22] and depending upon other factors (e.g. presence of children, access to parks, sandpits, etc.), the frequency of treatment for endoparasites should be at least four, up to 12 times per year, depending on the conditions, while treatment against ectoparasites should be done monthly. 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 significant parasitic infestations [23] [24] [25] [26] [27]. Additionally, most pet owners are not aware of the zoonotic potential of some parasites [28] [29]. Were pet owners aware, they might be more easily convinced to follow a rigorous schedule of treatment. Pet owner compliance with veterinary recommendations is critical to ensure timely treatment and control of parasites in dogs, and offering a highly palatable and preferred oral product does favor compliance and ultimately helps ensure control of parasitic infestations.

5. Conclusion

This study demonstrated that, when dogs were offered a choice between two commercially available formulations of endectoparasiticides, NexGard Spectra (afoxolaner and milbemycin oxime), formulated in a soft chewable tablet with braised beef flavoring and Simparica Trio (sarolaner, moxidectin and pyrantel), formulated as a pork-liver-flavored chewable tablet, significantly more dogs preferred NexGard Spectra.

Funding

This research was funded by Boehringer Ingelheim Animal Health.

Acknowledgements

We gratefully acknowledge the test facility staff of BerTek.

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. Simparica Trio[™] is a registered trademark of Zoetis.

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