Comparison of the acceptance of 2 anthelmintic formulations, in the dog

T. COURBET1, Dr S. BOUR1, Dr J. ROCHE2, Dr A. THIBAULT-FAYARD2*, Dr C. BODA3

1Bayer Santé, Service Développement & Affaires Réglementaires, Division Santé Animale, 13 rue Jean Jaurès 92807 PUTEAUX, FRANCE.
2Bayer Santé, Business Unit Animaux de Compagnie, Division Santé Animale, 13 rue Jean Jaurès 92807 PUTEAUX, FRANCE.
3Anistème Biosciences, 152, rue du clos des vignes, 34400 SAINT-CHRISTOL, FRANCE.

*Corresponding author: agnes.thibault@bayerhealthcare.com

SUMMARY

A study was conducted to compare the acceptance of two commercial formulations of broad-spectrum anthelmintics, Drontal® P meat taste and Dolpac® 10. The study took place in a professional breeding facility and involved 33 miniature and giant Schnauzer dogs aged 0.5 to 8.6 years. Body weight at inclusion ranged between 5 and 45 kg but all the dogs received one tablet on each study day as the purpose of the study was to assess voluntary consumption, not product efficacy. The study was based on a cross-over design with each of the two products being offered to all dogs on two study days in a random order. Drontal® P meat taste was significantly better than Dolpac® 10 in terms of voluntary and full consumption. In addition, the time for full Drontal® P meat taste ingestion was shorter than for Dolpac® 10. These results confirmed the satisfactory acceptance of the Drontal® P meat taste tablets by dogs. No product-related adverse events were observed during the study or the 7-day post-dosing follow-up period. Thanks to its original manufacturing process which incorporates the flavouring agent into the tablet, the Drontal® P meat taste product is readily accepted by dogs, and this enhances compliance and improves the control of zoonotic worm diseases.

Keywords: Acceptance, acceptance test, dewormer, dog, febantel, pyrantel, oxantel, praziquantel.

RÉSUMÉ

Cette étude a été conduite pour comparer, chez le chien, l’acceptance de deux formulations anthelminthiques, Drontal® P goût viande et Dolpac® 10. L’étude s’est déroulée dans un élevage de schnauzers nains et géants, avec des chiens âgés de 0.5 à 8.5 ans. Les chiens, qui pesaient entre 5 et 45 kg à l’inclusion, ont reçu chacun un comprimé de chaque produit. En effet, l’objectif de l’étude était d’évaluer l’acceptance des comprimés et pas l’efficacité. Le dosage n’avait pas d’importance. Selon la méthode du cross-over et de manière randomisée, chaque chien a reçu les deux comprimés au cours des deux jours d’étude. Les résultats ont montré que le comprimé Drontal® P goût viande est significativement mieux consommé, c’est-à-dire de manière spontanée et complète, que le comprimé de Dolpac® 10. De plus, les chiens avaient complétement le comprimé de Drontal® P goût viande en un temps significativement plus court par rapport au comprimé Dolpac® 10. Ceci confirme la bonne acceptation par le chien des comprimés de Drontal® P goût viande. De plus, aucun effet secondaire n’a été observé suite à l’administration des comprimés de vermifuge. Le mode de fabrication des comprimés de Drontal® P goût viande incorpore un arôme appétant “goût viande” directement dans la masse du comprimé, dès les premières étapes du processus de fabrication. Grâce à cette formulation originale, le comprimé de Drontal® P goût viande est bien accepté. On peut donc s’attendre à une amélioration de l’observance du traitement et à un meilleur contrôle des zoonoses parasitaires.

Mots-clés : Acceptance, test d’acceptance, vermifuge, chien, fébantel, pyrantel, oxantel, praziquantel.

Introduction

Endoparasites are commonly encountered in canine veterinary medicine, and several present in dogs have the potential to infect humans. According to a survey of pet owners in the Paris area, one dog out of four harbours intestinal parasites [3]. These include helminths, present in 12.9% of dogs, including roundworms (5.4%), hookworms (2.1%) and whipworms (5.4%). Intestinal parasites are more common in dogs living collectively, and the prevalence of intestinal worms in community kennels may reach 28%, with 24% of these animals presenting mixed infestations (two or more parasite species) [8].

In addition to the hazards posed by endoparasites in the animal community, humans may also become infected but owners are more conscious of possible contact injuries than the zoonotic risks stemming from their dog. Dog intestinal parasites raise serious public health concerns as the canine faecal contamination observed in urban areas increases the parasitic risk for humans [10]. Dogs are associated with various zoonotic diseases, including helminthiosis caused by Toxocara canis, Ancylostoma caninum and Trichuris vulpis [2, 5, 6]. Infestation by ascaris is most frequently observed in puppies whereas the prevalence of hookworms and whipworms is higher in adults, underlining the need to deworm dogs at all ages.

Current recommendations propose treating 2, 4, 6, 8, 10 and 12 weeks after birth for puppies, followed by treatment every month up to 6 months, then 2 to 4 times per year in adult dogs. Despite client education, poor veterinary compliance in applying appropriate deworming protocols would appear to persist [7, 11]. Compliance in veterinary medicine depends both on the dog and its owner. Poor compliance
often results from the veterinarian giving recommendations without any understanding of how the client is to apply them at home [7]. For instance, oral treatment in a dog may be fairly challenging for the owner, involving animal restraint, overcoming the animal's defence reactions, and the time required for force-feeding. This is also coupled with the psychological apprehension of treating their own pet. In addition, the dog may discard the tablet without the owner's knowledge. Oral deworming using palatable tablets ensures complete administration and therefore better compliance than with other oral formulations, while avoiding the need for an injection.

Substantial efforts have been made to minimise the risk of poor compliance during anthelmintic treatment, including quality information about zoonotic hazards for the owner and the use of highly palatable formulations of drugs intended for oral administration. Oral palatable formulations that are spontaneously accepted and consumed by the dog from a bowl are more convenient and enhance compliance with the anthelmintic treatment. Drontal® P meat taste (Bayer Santé, Division Santé Animale) is an oral tablet formulation used to prevent and treat helminth and nematode infestation in both puppies and dogs. The praziquantel, pyrantel and febantel active ingredients contained in Drontal® P meat taste are active against the worms implicated in the major zoonotic diseases, i.e. T. canis, A. caninum, T. vulpis and Echinococcus spp. Drontal® P meat taste was the first broad-spectrum anthelmintic agent (i.e. including the elimination of Taenia spp) marketed as an oral palatable tablet. The aim of the study described here was to assess dog acceptance of Drontal® P meat taste and compare its voluntary acceptance in dogs with a similar, broad-spectrum anthelmintic formulation containing praziquantel, oxantel and pyrantel (Dolpac® 10, Vetoquinol laboratory). Dolpac should be regarded as a negative control (non-palatable) vs Drontal® P meat taste (containing 50 mg praziquantel, 50 mg pyrantel (as embonate) and 49.94 mg pyrantel (as embonate), and 200.28 mg oxantel (as embonate); Vetoquinol).

All comparisons were based on the administration of a single tablet. It therefore follows that the individual dogs received different dosages (in mg/kg), which did not necessarily correspond to that recommended. However, the purpose of the study was to test the acceptance, not the efficacy, of the anthelmintic agents which both show a large safety margin.

The study was conducted as an acceptance test using a two-period cross-over design with a 7 day-wash out period. Each dog was offered one tablet of each of the two products independently to assess voluntary acceptance and consumption. The order in which the dog was offered the tablets, i.e., Drontal® P meat taste on the first day of testing and Dolpac® 10 on the second day, or vice versa was determined independently to assess voluntary acceptance and consumption. The order in which the dog was offered the tablets, i.e., Drontal® P meat taste on the first day of testing and Dolpac® 10 on the second day, or vice versa was determined by a randomised allocation plan. The randomisation was stratified according to breed (miniature Schnauzer and giant Schnauzer dogs) with 17 dogs (group 1) receiving Drontal® P meat taste on day 1 then Dolpac® 10 on day 8 and 16 dogs (group 2) receiving Dolpac® 10 on day 1 then Drontal® P meat taste on day 8.

This plan was designed in such a manner that each product was offered to about half the dogs on day 1 and half the dogs on day 8. Table 1 outlines study design and group composition.

### Materials and Methods

**ANIMALS SELECTION AND STUDY SITE**

The animals were selected from a professional breeder facility where animal accommodation met the requirements of the study protocol and the regulations in force.

The dogs continued to live under their routine conditions. They had unrestricted access to drinking water and were fed a commercial diet.

All the dogs were miniature or giant Schnauzers. Thirty-three dogs, 10 males and 23 females, were selected for inclusion in the study. At the start of the study the dogs were from 0.5 to 8.6 years old and weighed 5 to 45 kg.

Only dogs in good health with no concomitant diseases likely to impair appetite were included in the study. Exclusion criteria included pregnant or lactating females. In addition, dogs were withdrawn in the course of the study if not deemed able to comply with protocol requirements.

All the dogs had been previously vaccinated against at least canine distemper, hepatitis, parvovirus, and leptospirosis. They were acclimatised to their environment as the study took place in their usual home.

### STUDY DESIGN AND PROCEDURES

The investigational products consisted of Drontal® P meat taste (containing 50 mg praziquantel, 50 mg pyrantel (as embonate) and 150 mg febantel; Bayer Healthcare Animal Health) and Dolpac® 10 (containing 50 mg praziquantel, 49.94 mg pyrantel (as embonate), and 200.28 mg oxantel (as embonate); Vetoquinol).

All comparisons were based on the administration of a single tablet. It therefore follows that the individual dogs received different dosages (in mg/kg), which did not necessarily correspond to that recommended. However, the purpose of the study was to test the acceptance, not the efficacy, of the anthelmintic agents which both show a large safety margin.

The study was conducted as an acceptance test using a two-period cross-over design with a 7 day-wash out period. Each dog was offered one tablet of each of the two products independently to assess voluntary acceptance and consumption. The order in which the dog was offered the tablets, i.e., Drontal® P meat taste on the first day of testing and Dolpac® 10 on the second day, or vice versa was determined by a randomised allocation plan. The randomisation was stratified according to breed (miniature Schnauzer and giant Schnauzer dogs) with 17 dogs (group 1) receiving Drontal® P meat taste on day 1 then Dolpac® 10 on day 8 and 16 dogs (group 2) receiving Dolpac® 10 on day 1 then Drontal® P meat taste on day 8.

This plan was designed in such a manner that each product was offered to about half the dogs on day 1 and half the dogs on day 8. Table 1 outlines study design and group composition.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of dogs</th>
<th>Age range (years)</th>
<th>Body weight range (kg)</th>
<th>Gender</th>
<th>Day 1</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 dogs</td>
<td>0.5-8.6</td>
<td>6-38</td>
<td>12 females</td>
<td>Drontal® P meat taste</td>
<td>Dolpac® 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16 dogs</td>
<td>0.5-7.1</td>
<td>5-45</td>
<td>11 females</td>
<td>Dolpac® 10</td>
<td>Drontal® P meat taste</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 males</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Study groups and animal characteristics.
ACCEPTANCE TEST

Each dog was offered one tablet of the assigned product in a bowl placed on the floor, in the animal’s cage.

A timer was started at the moment the dog had access to the tablet in the bowl, and was stopped when the tablet was entirely swallowed.

The dogs were observed for 3 minutes after tablet intake to ensure that the product was not discarded. If the product was not taken after 30 minutes, the test was terminated.

Product consumption from the bowl was assessed as “spontaneously full” (the tablet was completely swallowed), “spontaneously partial” (the tablet was chewed and some pieces discarded) or “none” (the tablet was not swallowed at all) and was recorded for each test.

Consumption time was recorded as “consumption in 10 seconds or less” or “consumption in more than 10 seconds”.

Another criterion consisted of assessing any adverse events occurring in the 7 days following product administration.

The investigator also noted dog behaviour during the study such that any dogs showing excessive restlessness and no interest in the product were withdrawn from the study. Animals selection for an acceptance test is crucial as bias may be due to individual dog behaviour with some eating everything and others systematically refusing everything.

GENERAL PROCEDURES

The two products tested in the study were stored according to the manufacturer’s recommendations. In order to perform the acceptance test, the Investigator removed the tablet from the blister package, taking care not to touch it with his hands.

The dogs were fasted for 6 hours before the start of the test and the experiment was performed at approximately the same time on each study day (day 1 and day 8).

Once the study had been completed, the dogs returned to their normal activities and were monitored for 7 days.

STATISTICAL ANALYSIS

The dog was considered as the experimental unit.

For each intake mode (“spontaneous full”, “spontaneous partial” and “none”), the number of dogs was described as a relative frequency (percentage) for each study day and over day 1 and day 8. Data were presented as histograms. Product, period and sequence effects were tested using a generalised linear model.

A Mc Nemar’s test with continuity correction was used to assess any difference in consumption between the two products at the 5% level of statistical significance.

Numbers of “spontaneous full” ingestion in “10 seconds or less” or “more than 10 seconds” were described as relative frequencies for each product. Only the time for “spontaneous full” intake was analysed, assuming that “spontaneous partial” consumption always took more than 10 seconds given that the tablet was successively ingested and discarded before being partially swallowed. Mc Nemar’s test with continuity correction was used to assess any difference in the time for “spontaneous full” consumption between the two products at the 5% level of statistical significance.

Results

ACTUAL GROUP SIZE

A total of 33 miniature and giant schnauzers participated the study. A total of 62 individual acceptance tests were conducted on the two study days (days 1 and 8) with thirty-two dogs being offered a Drontal® P meat taste tablet and thirty dogs being offered a Dolpac® 10 tablet.

The details of dogs participating in the two study days, along with the reasons for exclusions, are given in Table 2.

As the statistical analysis used Mc Nemar's test on paired data, dogs that were absent on one of the two study days were excluded from the analysis.

Therefore, the results analysed statistically concerned 29 dogs in all, 16 in group 1 and 13 in group 2. By contrast, the descriptive analysis involved all the dogs (32 tests conducted with Drontal® P meat taste and 30 tests conducted with Dolpac® 10).

ACCEPTANCE RESULTS

Of the 17 dogs offered a Drontal® P meat taste tablet on day 1, 16 (94%) fully consumed the tablet and one (6%) did not consume the tablet at all.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of selected dogs</th>
<th>Number of missing dogs over the two study days</th>
<th>Day 1</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>1</td>
<td>Drontal® P meat taste n=17</td>
<td>Dolpac® 10 n=16**</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>3</td>
<td>Dolpac® 10 n=14*</td>
<td>Drontal® P meat taste n=15***</td>
</tr>
</tbody>
</table>

* One dog was deemed too restless and one dog was absent on that day
** One dog was pregnant
*** One dog was withdrawn from the facility

Table II : Details of dogs participating in each study day.
Of the 14 dogs offered a Dolpac® 10 tablet on the same day, 6 (43%) fully consumed the tablet, 3 (21%) partially consumed the tablet and 5 (28%) refused the tablet.

Of the 15 dogs offered a Drontal® P meat taste tablet on the same day, all (100%) fully consumed the tablet.

Of the 16 dogs offered a Dolpac® 10 tablet on day 8, 6 (37.5%) fully consumed the tablet and 10 (62.5%) totally refused the tablet.

The results for tablet intake on each study day and for each product are presented in figure 1.

No significant day-to-day difference (period effect) was detected for intake mode of either product (p=0.298), suggesting that the test day did not affect product acceptance. Also, the order in which the two products were offered (sequence effect) had no effect on the results (p=0.284).

A total of 32 individual tests were performed with Drontal® P meat taste on the two study days. Thirty-one dogs (97%) spontaneously and fully consumed the tablet and one dog (3%) totally refused the tablet.

A total of 30 individual tests were performed with Dolpac® 10 on the two study days. Twelve dogs (40%) totally accepted to consume the tablet, 3 (10%) partially consumed the tablet and 15 (50%) totally refused the tablet.

The results for tablet ingestion on day 1 and day 8 are presented in figure 2 and in table 3 for both products.

The difference in spontaneous full consumption between the two products was significant, showing greater spontaneous full consumption with Drontal® P meat taste tablets than with Dolpac® 10 tablets (p<0.01) (see Table 4).

Of the 31 dogs that spontaneously and fully ingested the Drontal® P meat taste tablets, 18 (58%) swallowed the tablet in 10 seconds or less and 13 (42%) in more than 10 seconds. Of the 12 dogs that spontaneously and fully ingested the Dolpac® 10 tablets, none (0%) swallowed the tablet in 10 seconds or less. It took all dogs more than 10 seconds to fully and spontaneously ingest the Dolpac® 10 tablets (see figure 3 and table 5).
The difference in time for spontaneous full consumption between the two products was significant \((p<0.01)\). No dogs fully consumed Dolpac® 10 tablets in 10 seconds or less (see Table 6).

### SAFETY

No adverse events related to the administration of the Drontal® P meat taste tablet or the Dolpac® 10 tablet were recorded in the course of the study or the 7-day post-dosing follow-up period. The products were well tolerated in all the dogs at doses up to twice the recommended dose.

### Discussion

The Drontal® P meat taste tablets were voluntarily and fully accepted by the dogs on both study days, and this acceptance was significantly better than that of the Dolpac® 10 tablets. In addition, the time required to fully ingest the Drontal® P meat taste tablets was 10 seconds or less in 58% of cases whereas it took all dogs more than 10 seconds to fully consume the Dolpac® 10 tablets.

No guidelines are currently available describing the minimum requirements for the assessment of drug palatability. However, it is important to note that the procedure used for the study reported in this paper is an adaptation of previous schemes used by the pet food industry [12]. Such a design has previously been used to assess the acceptance of pharmaceutical formulations in dogs, and gives reliable results [9, 12]. We did know the outcome for Dolpac 10 (negative control) but not for Drontal P meat flavour. Actually, the aim of the study was to clearly demonstrate that the new manufacture procedure used in Drontal P meat taste flavour was efficient in masking bitter-taste agent.

In addition, despite small group sizes, the Investigator made every effort to select dogs representing large and small size breed, as well as dogs of various ages, with the aim of reducing bias.

The results obtained in this study are consistent with the levels of acceptance observed in previous studies performed with palatable formulations of carprofen in dogs. These studies used a similar design and concluded that the product was well accepted with full consumption in 91 to 98% of the dogs [9]. Consequently, the results obtained in this study, and the conclusion that the acceptance of the Drontal® P meat taste product is satisfactory in dogs, are both reliable. The adaptation of the acceptance study design used in the pet food industry included the recording of the time interval between product offering and ingestion, thus documenting the dog's level of interest. With regard to this criterion, the degree of dog enthusiasm was significantly greater when offered the Drontal® P meat taste tablets than when offered the Dolpac® 10 tablets.

Palatable formulations can improve compliance both by the owner and the dog if the drug has a strong odour or an unappealing taste. Praziquantel has a bitter taste [1] thus

---

**Table IV**: Time for spontaneous full consumption of Drontal® P meat taste and Dolpac® 10 tablets in the dogs included in the statistical analysis.

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of dogs that fully consumed the tablet</th>
<th>Number of dogs that spontaneously and fully consumed he tablet in 10 seconds or less</th>
<th>Number of dogs that spontaneously and fully consumed the tablet in more than 10 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drontal® P meat taste</td>
<td>28</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Dolpac® 10</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

**Table V**: Statistical analysis of time for spontaneous full consumption of the Drontal® P meat taste and Dolpac® 10 tablets.

<table>
<thead>
<tr>
<th>Number of dogs that spontaneously and fully consumed the Dolpac® 10 tablet in 10 seconds or less</th>
<th>Number of dogs that fully consumed the Drontal® P meat taste tablet in more than 10 seconds</th>
<th>Total</th>
<th>P value for McNemar’s test (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0002</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>12</td>
<td>28</td>
</tr>
</tbody>
</table>
making it difficult to entice dogs to swallow the medication. Drontal® P meat taste is the palatable formulation of the praziquantel-pyrantel-febantel fixed formulation intended to be used as a broad-spectrum dewormer in dogs. In this study, we aimed to compare the acceptance of Drontal® P meat taste with that of an anthelmintic agent currently marketed in France for dogs, and also containing the bitter tasting praziquantel active ingredient (Dolpac® 10).

Active agents with a bitter or bad taste are masked by adding an appropriate flavouring agent. A number of flavouring excipients have been successfully used in veterinary medicinal product, e.g. beef, pork and lamb, that are preferred by dogs to chicken, liver or horse meat [12]. The artificial beef flavour contained in Drontal® P meat taste was chosen based on dog taste preferences and on its previously successful uses in veterinary medicinal products.

The manufacturing process can also have an impact on palatability. For instance, flavor enhancers may be added according to three general taste-masking principles: application of a physical barrier (coating or microencapsulation using polymers), solubility modification (using ion exchange or complexation) and solid dispersions (the drug is dispersed in a polymer solution then solidified, e.g. by melt-granulation) [4]. Each of these three principles is subdivided into several methods.

Drontal® P meat taste is formulated by embedding the beef flavour into the mass formed by the active ingredients and the other excipients very early in the manufacturing process. This masks praziquantel’s bitter taste and strong smell even though the tablet is chewed by the dog and results in a high level of spontaneous and full tablet consumption as observed in the study reported here (97%). When dealing with active ingredients that have a bitter taste or a strong smell, such as praziquantel, an incorporation process is obviously essential. Acceptance tests conducted with the non palatable formulation containing praziquantel (Dolpac® 10) showed that 10% of the dogs partially consumed the tablet (chewing and rejection), suggesting taste-related refusal. By contrast, none of the dogs spat out the Drontal® P meat taste tablet after chewing.

Conclusion

Both spontaneous full consumption and tablet ingestion time were better with Drontal® P meat taste tablets than with Dolpac® 10 tablets. In the absence of a standard method for designing acceptance studies, the present study was conducted according to a design used in the pet food industry that has proved to be reliable in previous experiments. Acceptance tests conducted with pharmaceutical products assess the consumption of a medication and are therefore a direct measure of compliance. Therefore, it may be concluded that Drontal® P meat taste presents a high level of acceptance in the dog, consistent with improved compliance and control of zoonotic helminthic diseases.

References


