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Palatability for Dogs of Two Beef-based Chewable Formulations in a Branded Drug 'Cardomec Chewable P' and a Japanese Generic Drug 'Ivermec PI' Containing Ivermectin and Pyrantel Embonate as Active Ingredients

Yukari NAKAMURA and Tohru FUKASE

Department of Veterinary Medicine, Faculty of Veterinary Medicine,
Okayama University of Science,
1-3 Ikoi-no-oka, Imabari-shi, Ehime 794-8555, Japan

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For 200 dogs, the degrees of palatability of two beef-based chewable formulations were compared: 'Cardomec Chewable P' aggregate (Boehringer Ingelheim Animal Health Japan Co., Ltd., Tokyo, Japan) and 'Ivermec PI' aggregate (Fujita Pharmaceutical Co., Ltd., Tokyo, Japan). They respectively contained ivermectin and pyrantel embonate (pyrantel pamoate) as active ingredients. Of the 200 dogs, 192 (96%) voluntarily consumed 'Cardomec Chewable P' within 1–25 (median 6) s; 197 (98.5%) voluntarily consumed 'Ivermec PI' within 1–21 (median 4) s. When the two drugs were presented simultaneously to the 200 dogs, 78 dogs consumed 'Cardomec Chewable P' and 119 dogs consumed 'Ivermec PI'. Three dogs consumed neither drug. Results show that the 'Ivermec PI' palatability is higher than that of 'Cardomec Chewable P' in dogs. This difference in palatability is inferred as deriving from different varieties and qualities of beef used as a pharmaceutical excipient when compounding and formulating the chewable products.

Keywords: chewable formulation, dog, ivermectin, palatability, pyrantel embonate.

1. Introduction

Chewable formulations containing ivermectin and pyrantel embonate (pyrantel pamoate) as active ingredients have been used extensively worldwide for prophylaxis of canine heartworm disease and for elimination of roundworms and hookworms in dogs [4, 5, 15, 16, 18, 19]. Generic drugs incorporating these ingredients have been developed in many countries, including Japan [7]. Most of these generic drugs, similarly to the branded drug, were developed for administration as chewable formulations [7], intended primarily for voluntary consumption by dogs. The generic drugs are thought to be equivalent to the branded drug in their efficacy [8, 17]. However, their respective degrees of palatability differ among the different chewable formulations because the varieties and qualities of meats such as beef, which are compounded to constitute chewable formulations, differ among the drugs.

We previously examined the respective degrees of palatability of the branded drug of this formulation and one generic drug of Japanese manufacturer. Results demonstrated that 97% and 99% of the dogs voluntarily consumed each drug, respectively [10, 14]. For those studies, however, each study examined different dogs for the branded and the generic product. In fact, the degrees of palatability of the two drugs were not compared directly. This study was conducted to compare the degrees of palatability of the two drugs using each drug with the same dog.

2. Materials and Methods

2-1 Drugs

The branded drug and the generic drug of Japanese manufacturer, which respectively contained ivermectin and pyrantel embonate as active ingredients, were evaluated. The original drug aggregate is configured with 'Cardomec Chewable P 34', 'Cardomec Chewable P 68', 'Cardomec Chewable P 136', and 'Cardomec Chewable P 272' (Boehringer Ingelheim Animal Health Japan Co., Ltd., Tokyo, Japan). The generic drug aggregate is configured with 'Ivermec PI-34', 'Ivermec PI-68', 'Ivermec PI-136', and 'Ivermec PI-272' (Fujita Pharmaceutical Co., Ltd., Tokyo, Japan).

Contents of ivermectin and pyrantel embonate were 34 μg and 81 mg, respectively, in 'Cardomec Chewable P 34' (about 2.47 g) and 'Ivermec PI-34' (about 2.3 g), 68 μg and 163 mg, respectively, in 'Cardomec Chewable P 68' (about 4.95 g) and 'Ivermec PI-68' (about 4.6 g), 136 μg and 326 mg, respectively, in 'Cardomec Chewable P 136' (about 6.43 g) and 'Ivermec PI-136' (about 5.5 g), and 272 μg and 652 mg, respectively, in 'Cardomec Chewable P 272' (about 7.53 g) and 'Ivermec PI-272' (about 6.0 g). Both of the two drug aggregates contain beef in their pharmaceutical excipients to formulate the chewable formulations, with the expectation of achieving high palatability in dogs.

2-2 Animals

This study, conducted in Japan, examined 200 dogs of various breeds, 105 females of which 57 had been ovariohysterectomized or ovariectomized and 95 males of which 47 had been orchiectomized, 3 months to 14 years old, with 2.9–38.5 kg of body weight.

The dogs were those of juveniles which had not experienced an infection season of *Dirofilaria immitis*, those which were considered not to have been parasitized by *D. immitis* based on the infallible medicine history of prophylactic drugs, or those confirmed to be negative in both microfilariae and adult antigen of *D. immitis*. At that time, detection of microfilariae was done by acetone testing of concentration method examining anticoagulated whole blood with ethylenediaminetetraacetic acid dipotassium salt (EDTA-2K) after collection from the cephalic vein of the left or right forelimb. The adult antigen was tested using a test kit (SNAP Heartworm RT Test; IDEXX Laboratories, Inc., Tokyo, Japan), using the serum separated by conventional means after blood collection from the same vein as described above.

Administration of the evaluated drugs was planned as a usual and routine prophylactic procedure against dirofilariasis in each dog at each guardian's home based on agreement of each guardian. Rearing conditions such as locations and foods were not changed for this study. They were the same as those used before. No veterinary treatment was given to dogs during the study, except for administration of the evaluated drugs.

2-3 Procedures for evaluating voluntary consumption of drugs by dogs

The dogs were grouped to 100 replicates, consisting of two animals each, in the order of induction to the study. The two dogs of each replicate were then assigned randomly to the two test groups using a random number table of our own making with C language. Dogs of one group (test group A) were first administered 'Cardomec Chewable P' and secondly 'Ivermec PI'. Dogs of the other group (test group B) were first administered 'Ivermec PI' and secondly 'Cardomec Chewable P'. The two administrations of medications were done with one-month intervals.

The administration of the drugs was done for the respective dogs at three hours after feeding of their routine diets. The drug was presented under the nose of each dog. The time (seconds) until the dog voluntarily took the drug was measured. For cases in which the dog did not consume the drug within 30 s, the drug was judged as 'not consumed'. Furthermore, when the whole of the drug was not swallowed or a part of the drug was expelled by the dog, the drug was also judged as 'not consumed', even if the dog voluntarily ingested the drug once.

Dosages of 'Cardomec Chewable P' and 'Ivermec PI' were based on the recommendation of the drugs: prescribed administration reference quantities of 6 μg/kg body weight for ivermectin and 14.4 mg/kg for pyrantel embonate. Therefore, 'Cardomec Chewable P 34' or 'Ivermec PI-34' was presented to dogs with body weight of 5.6 kg or less, 'Cardomec Chewable P 68' or 'Ivermec PI-68' was presented to dogs with

body weight of 5.7–11.3 kg, 'Cardomec Chewable P 136' or 'Ivermec PI-136' was presented to dogs with body weight of 11.4–22.6 kg, and 'Cardomec Chewable P 272' or 'Ivermec PI-272' was presented to dogs with body weight of 22.7–45.3 kg.

2-4 Procedures for evaluating selectivity of drugs by dogs

At one month after the study described above for evaluating voluntary consumption, the 200 dogs' selection of drugs was assessed. The two drugs, 'Cardomec Chewable P' and 'Ivermec PI', were presented simultaneously under the nose of each dog. Which drug was consumed voluntarily by the dog was observed.

For this examination, the two drugs were put on a plastic-made tray of 50 cm × 30 cm at a distance of 30 cm between the two drugs. Presentation of the drugs was adapted for equalization of interest of dogs against the two drugs: the midline of the distance separating the two drugs was brought under the dog's nose.

After consumption of one drug by the dog, the tray was removed immediately from the front of the dog to avoid consumption of both presented drugs. When neither of the two was consumed by a dog during 30 s, a judgment was made that 'the drugs were not consumed'.

2-5 Observation of adverse events

General findings of the dogs were observed carefully and circumstantially by each guardian during the day of drug administration and the next day to note any adverse event.

2-6 Ethics

Medications used for this study were done as a usual and routine prophylactic procedure against dirofilariasis and are therefore a necessary clinical treatment. In addition, the dogs were all treated with due consideration of animal welfare during the research based on the "Regulations for Animal Experimentation at the General Incorporated Association, Katsuragi Institute of Life Sciences" (authors' former affiliation) under approval by the Institutional Animal Care and Use Committee.

3. Results

3-1 Voluntary consumption of drugs by dogs

For test group A, in which dogs were first tested with 'Cardomec Chewable P' and secondly with 'Ivermec PI', 95 and 98 of the 100 dogs voluntarily

Table 1 Voluntary consumption of the branded drug 'Cardomec Chewable P' by dogs

Drugs	No. dogs used	Dogs voluntarily consuming the drug		Time (s) until dogs voluntarily consume the drug*				
		No. dogs	Proportion (%)	Minimum	First quartile	Median	Third quartile	Maximum
Test group A								
'Cardomec Chewable P 34'	23	19	83	2	4	6	7.5	25
'Cardomec Chewable P 68'	35	34	97	2	4.25	6	9	21
'Cardomec Chewable P 136'	28	28	100	2	5	6	8.25	17
'Cardomec Chewable P 272'	14	14	100	2	4.25	6.5	7	8
Subtotal	100	95	95	2	4.5	6	8	25
Test group B								
'Cardomec Chewable P 34'	20	18	90	2	4.25	6.5	8	23
'Cardomec Chewable P 68'	28	27	96	1	3	6	8	24
'Cardomec Chewable P 136'	30	30	100	1	4.25	7	8	13
'Cardomec Chewable P 272'	22	22	100	2	4.25	6	7	16
Subtotal	100	97	97	1	4	6	8	24
Test group A+B								
'Cardomec Chewable P 34'	43	37	86	2	4	6	8	25
'Cardomec Chewable P 68'	63	61	97	1	4	6	9	24
'Cardomec Chewable P 136'	58	58	100	1	5	7	8	17
'Cardomec Chewable P 272'	36	36	100	2	4	6	7	16
Sum total	200	192	96	1	4	6	8	25

* Time (s) until dogs voluntarily consume 'Cardomec Chewable P' was significantly ($p<0.05$) longer than that for 'Ivermec PI' (see Table 2).

Table 2 Voluntary consumption of the generic drug 'Ivermec PI' by dogs

Drugs	No. dogs used	Dogs voluntarily consuming the drug		Time (s) until dogs voluntarily consume the drug*				
		No. dogs	Proportion (%)	Minimum	First quartile	Median	Third quartile	Maximum
Test group A								
'Ivermec PI-34'	23	21	91	1	2	3	4	17
'Ivermec PI-68'	35	35	100	1	3	4	7	12
'Ivermec PI-136'	28	28	100	1	3	5	6	11
'Ivermec PI-272'	14	14	100	1	4.25	5	6	8
Subtotal	100	98	98	1	3	4	6	17
Test group B								
'Ivermec PI-34'	20	19	95	2	3	5	6.5	21
'Ivermec PI-68'	28	28	100	1	2	3.5	6	16
'Ivermec PI-136'	30	30	100	1	3	3.5	6	7
'Ivermec PI-272'	22	22	100	1	2	3.5	5	15
Subtotal	100	99	99	1	2	4	6	21
Test group A+B								
'Ivermec PI-34'	43	40	93	1	2	3	5.25	21
'Ivermec PI-68'	63	63	100	1	2	4	6.5	16
'Ivermec PI-136'	58	58	100	1	3	4.5	6	11
'Ivermec PI-272'	36	36	100	1	2.75	4	5.25	5
Sum total	200	197	98.5	1	2	4	6	21

* Time (s) until dogs voluntarily consume 'Ivermec PI' was significantly ($p<0.05$) shorter than that for 'Cardomec Chewable P' (see Table 1).

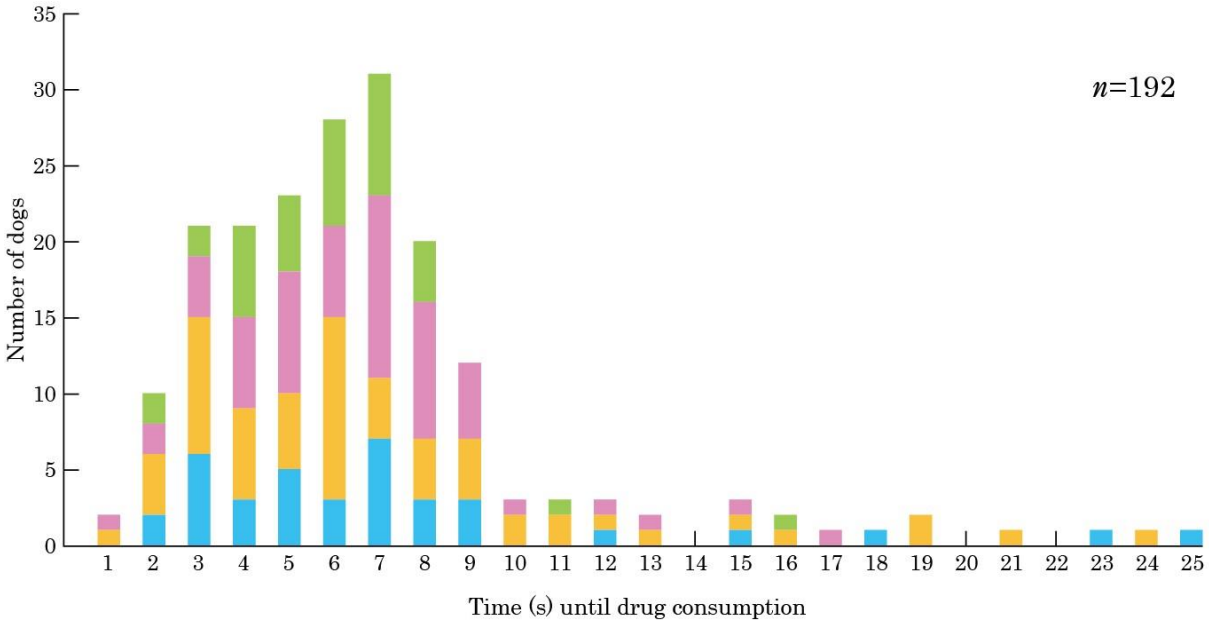

Fig. 1 Frequency distribution of the times until voluntary consumption of the branded drug 'Cardomec Chewable P' by dogs

'Cardoemc Chewable P 34', 'Cardoemc Chewable P 68',
'Cardoemc Chewable P 136', 'Cardoemc Chewable P 272'

The figure is drawn after excluding eight dogs that did not consume voluntarily the drug.

consumed 'Cardomec Chewable P' and 'Ivermec PI', respectively. All the dogs were confirmed to have swallowed the entire drug completely when they had once taken the drug in the mouth. The times until the

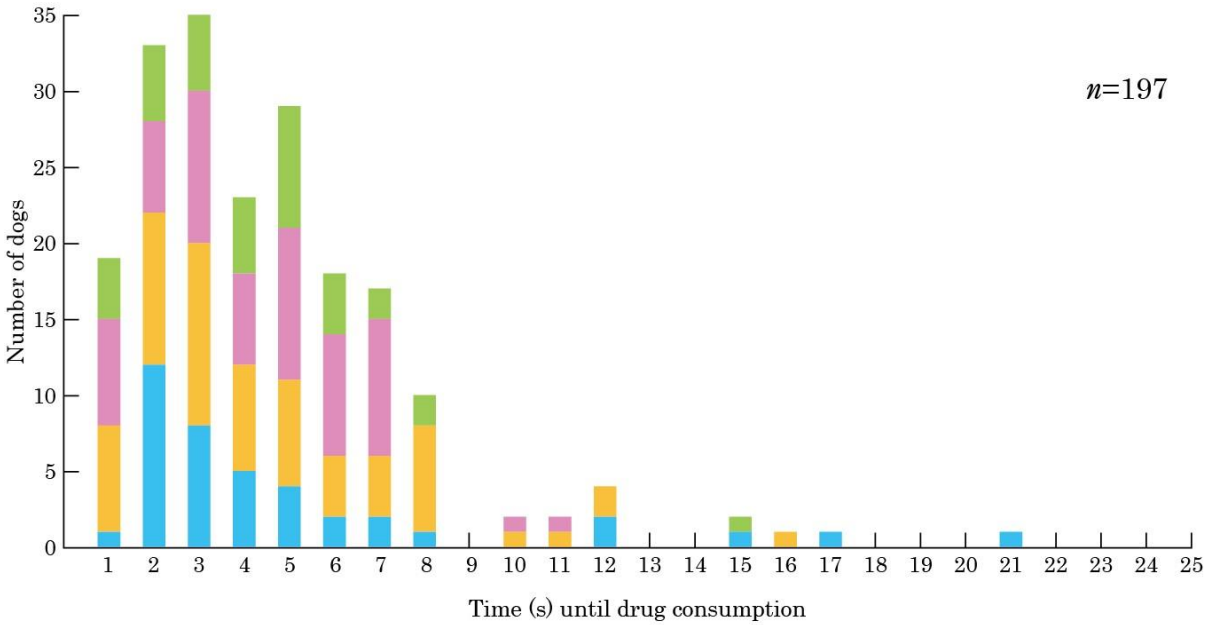

Fig. 2 Frequency distribution of the times until voluntary consumption of the generic drug 'Ivermec PI' by dogs

'Ivermec PI-34', 'Ivermec PI-68', 'Ivermec PI-136', 'Ivermec PI-272'

The figure is drawn after excluding three dogs that did not consume voluntarily the drug.

dogs voluntarily took the drug were 2–25 (6 in median) s for 'Cardomec Chewable P' and 1– 17 (4 in median) s for 'Ivermec PI' (Tables 1 and 2).

For test group B, in which dogs were first tested with 'Ivermec PI' and secondly with 'Cardomec Chewable P', 99 and 99 of the 100 dogs voluntarily consumed 'Ivermec PI' and 'Cardomec Chewable P', respectively. Furthermore, in this test group, as with test group A, all the dogs were confirmed to have swallowed the entire drug completely when they had once taken the drugs in the mouth. The times until the dogs voluntarily consumed the drug were 1–21 (4 in median) s for 'Ivermec PI' and 1–24 (6 in median) s for 'Cardomec Chewable P' (Tables 1 and 2).

Comparison of the results in test groups A and B revealed no differences in the number of dogs consuming each drug and the times until voluntary consumption of the drugs. Based on this information, results in the two test groups were added together as follows. The numbers of dogs which voluntarily consumed the drugs were 192 (96%) for 'Cardomec Chewable P' and 197 (98.5%) for 'Ivermec PI'. No significant difference was found between the numbers of these dogs by chi-square testing with a

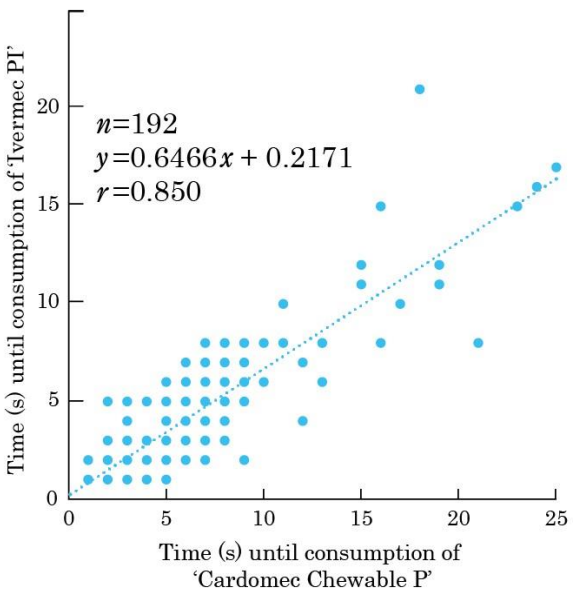

Fig. 3 Correlation between times until voluntary consumption of the branded drug 'Cardomec Chewable P' and the generic drug 'Ivermec PI' by dogs

The figure is drawn after excluding eight dogs that did not voluntarily consume either drug. Duplicate dots are omitted from the figure.

Table 3 Summary of dogs that did not voluntarily consume the branded drug ‘Cardomec Chewable P’ and/or the generic drug ‘Ivermec PI’

Breed	Sex*1	Age*2	Body weight (kg)	Drug presented*3	Consumed or not*4		Unbalanced diet*5
					‘Cardomec Chewable P’	‘Ivermec PI’	
Chihuahua	Female (neutered)	2 y	3.5	34 μg product	×	○	+
Poodle (Toy)	Male (neutered)	4 y	2.9	34 μg product	×	×	+
Poodle (Toy)	Female	2 y	3.4	34 μg product	×	○	−
Miniature Schnauzer	Male (neutered)	1 y	6.8	68 μg product	×	○	+
Dachshund (long-haired miniature)	Female (neutered)	2 y	4.1	34 μg product	×	○	−
Dachshund (long-haired miniature)	Female (neutered)	10 m	4.0	34 μg product	×	×	+
Chihuahua	Male	1 y	3.1	34 μg product	×	×	+
French bulldog	Female (neutered)	3 y	9.2	68 μg product	×	○	+

*1 Neutered: ovariohysterectomized or ovariectomized females, orchiectomized males
*2 y, years; m, months
*3 Expressed as ivermectin contents
*4 ○, consumed; ×, not consumed
*5 Based on an interview with the guardian: +, with a tendency to an unbalanced diet; −, without a tendency to an unbalanced diet

significance level set at 5%. The times until voluntary consumption were 1–25 (6 in median) s for ‘Cardomec Chewable P’ and 1–21 (4 in median) s for ‘Ivermec PI’ (Tables 1 and 2). The frequency distribution of the times until voluntary consumption for each drug, as shown in Figs. 1 and 2, revealed that many dogs consumed ‘Cardomec Chewable P’ within 4–8 s (first quartile–third quartile, see Table 1) and consumed ‘Ivermec PI’ within 2–6 s (first quartile–third quartile, see Table 2). The times for ‘Ivermec PI’ were found to be significantly shorter than those for ‘Cardomec Chewable P’ by Wilcoxon rank sum test at a significance level of 5%.

High correlation was confirmed between the times until voluntary consumption for ‘Cardomec Chewable P’ and ‘Ivermec PI’, with a correlation coefficient (r) of 0.850. However, many dogs consumed ‘Ivermec PI’ within a shorter time than ‘Cardomec Chewable P’, as reflected by the regression coefficient or the regression line slope (Fig. 3).

Eight dogs did not consume ‘Cardomec Chewable P’ voluntarily. Three of the eight dogs did not also consume ‘Ivermec PI’. Many dogs which did not consume the drugs were small-breed dogs. Interviews with the guardians of these dogs demonstrated that six of the eight dogs showed an unbalanced diet in ordinary feeding and did not accept foods of many varieties, although they did not dislike meats (Table 3).

3-2 Selectivity of drugs by dogs

When presenting the two tested drugs simultaneously to the 200 dogs, 78 and 119 dogs respectively chose ‘Cardomec Chewable P’ and ‘Ivermec PI’. Three dogs consumed neither drug. The number of dogs which chose ‘Ivermec PI’ was found to be significantly larger than the number which chose ‘Cardomec Chewable P’ by chi-square testing at a significance level of 5% (Table 4).

3-3 Adverse events

No dogs showed changes in activity, appetite, or other general findings. They did not develop symptoms such as tremor, sialorrhea, vomition, and diarrhea after taking the drugs. The dogs developed no abnormality such as roughing of the hair coat, alopecia, or skin redness.

4. Discussion

Ivermectin, a macrocyclic compound, shows high killing effects for various parasite species of nematodes and arthropods [3]. Pyrantel embonate has been known as an antiparasitic drug mostly against gastrointestinal nematodes [12]. In veterinary medicine for small animal practice, ivermectin and

Table 4 Selectivity of the branded drug 'Cardomec Chewable P' and the generic drug 'Ivermec PI' when presented simultaneously to dogs

Body weight of dog*1	Drugs presented*2	No. dogs used	No. dogs which consumed		
			'Cardomec Chewable P'	'Ivermec PI'	None
5.6 kg or less	34 μg product	43	14	26	3
5.7–11.3 kg	68 μg product	63	22	41	0
11.4–22.6 kg	136 μg product	58	23	35	0
22.7–45.3 kg	272 μg product	36	19	17	0
Total		200	78	119*3	3

*1 Dog body weights were rounded off to the second decimal place when measured.
*2 Expressed as ivermectin contents
*3 Significantly more dogs chose 'Ivermec PI' ($p<0.05$) than the theoretical value.

pyrantel embonate have been used chiefly as a prophylactic agent against canine dirofilariasis [1, 2] and as an anti-parasitic agent against roundworms and hookworms [12], respectively, in dogs and domestic cats. The drugs evaluated in the present study were a branded drug 'Cardomec Chewable P' and its generic drug 'Ivermec PI', both of which use ivermectin and pyrantel embonate as active ingredients and which have been manufactured as beef-based chewable formulations for prophylaxis of canine dirofilariasis and also for elimination of gastrointestinal roundworms and hookworms [7].

The chewable formulation is a characteristic dosage form in a category of veterinary drugs. It is designed to be consumed voluntarily by dogs and cats by containing highly preferred component(s) such as beef, chicken, and other animal/plant materials as a part of pharmaceutical excipients. Drugs formulated in a chewable form are expected to be very convenient, especially in the case of drugs such as prophylactics against dirofilariasis, which are often administered to animals by their guardians in their home. However, it is desirable that the palatability of the drugs will be confirmed before prescribing them for animals.

We earlier reported the high palatability of 'Cardomec Chewable P' and 'Ivermec PI', with the results that the drugs were consumed voluntarily, respectively, by 97 of 100 dogs and by 198 of 200 dogs [10, 14]. By contrast, these two trials were conducted separately using different dogs. The palatability of the two drugs had not been compared directly in any prior study. To compare the palatability of the two drugs, this study used the same dogs for evaluating the voluntary consumption of the drugs, and obtained the results that 'Cardomec Chewable P' and 'Ivermec PI' were voluntarily consumed, respectively, by 96% and 98.5% of the dogs. These results corresponded well with those obtained from our early studies [10, 14].

When comparing the times until the dogs consume 'Cardomec Chewable P' and 'Ivermec PI', first quartile, second quartile (median), and third quartile were 4 s, 6 s, and 8 s for the former, and 2 s, 4 s, and 6 s for the latter drug. These results were also almost identical to those used in earlier studies [10, 14].

Based on the facts in our early studies described above [10, 14] and results of the present study, it is considered that the palatability of the drugs is higher for 'Ivermec PI' than 'Cardomec Chewable P'. The higher palatability of 'Ivermec PI' is expected to be bolstered from results obtained for selectivity in the present study.

Some dogs voluntarily consumed only one or neither drug. Many of these dogs were known to have an unbalanced diet, according to their guardians. Avoidance of drug consumption might have been unavoidable in a few dogs.

The two evaluated drugs, 'Cardomec Chewable P' and 'Ivermec PI', contain the same active ingredients with the same contents. They use beef as a pharmaceutical excipient. However, the respective origins and qualities of the beef should be considered as different between the two drugs. Other excipients are also thought to be different between the two [9]. Differences in the palatability of the two drugs in dogs are thought to be attributable to differences in the excipients, such as beef. Regarding voluntary consumption, the times until the intake might not be important. However, quicker consumption of the drug will engender the reduction of time and effort for

medication.

With respect to the safety of the evaluated drugs, although only general findings were observed macroscopically in this study, no adverse event was noticed. Considering past reports of the safety of the branded [5] and this generic [6] drugs, there was no apprehension about medication using the drugs.

Food allergies have attracted notice in recent years in dogs; some dogs are known to have beef allergies [11, 13, 20], although no dogs examined for this study developed allergy symptoms after medication. The branded drug with beef-based chewable formulations of ivermectin and pyrantel embonate has been used worldwide for many years [4, 5, 15, 16, 18, 19], without remarkable trouble with food allergy. Accordingly, the possibility is slight that the drugs developed beef allergy symptoms in dogs. However, for dogs that had been diagnosed as having beef allergies, sufficient attention must be devoted in case something happens.

The evaluated chewable products will often be administered for prophylaxis of canine dirofilariasis, rather than for elimination of roundworms and hookworms. For heartworm prevention, the drug is administered to dogs once a month for at least 6–7 months each year, from one month after appearance to one month after disappearance of mosquitoes, mostly at home by their guardians. The drugs which are consumed voluntarily by animals are expected to be quite convenient because they will be treated easily even by guardians who are not experienced with administering medication.

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