An evaluation of the relative palatability of two commercial oral tablet formulations of carprofen and meloxicam in dogs using acceptance and preference tests

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SUMMARY

It is recognised that dosing compliance for orally administered therapies in small animal veterinary medicine is often sub-optimal. The palatability of an oral product can be a significant factor in improving dosing compliance, especially in situations where the drug must be administered daily over an extended period of time. Veterinarians often lack information regarding the relative palatability of products when prescribing a course of therapy. Two palatability studies, one using acceptance tests and one using preference tests were conducted in order to evaluate the relative palatability of commercial palatable oral tablet formulations of two non-steroidal anti-inflammatory drugs (NSAIDS) – carprofen palatable tablets (Rimadyl® Palatable Tablets) and meloxicam chewable tablets (Metacam® Chewable Tablets for Dogs). In the acceptance tests, voluntary full consumption of carprofen palatable tablets occurred on 97.8% of the occasions on which they were offered, compared with 13.0% for meloxicam chewable tablets ($P < 0.0001$). When offered a choice of the two products in a preference test procedure, more than 95% of dogs chose carprofen palatable tablets in preference to meloxicam chewable tablets ($P < 0.0001$). Thus it is a reasonable expectation that, in clinical situations, prescription of carprofen palatable tablets will ensure enhanced dosing compliance and this should assist in achieving the intended clinical outcomes.

Keywords: Dosing compliance, palatability, acceptance tests, preference tests, carprofen, meloxicam, dog.

RÉSUMÉ

Évaluation comparée de la palatabilité de comprimés appétents de carprofène et de méloxicam chez le chien par des tests d'acceptance et de préférence

Il est admis que l'observance thérapeutique à l'égard de médicaments administrés par voie orale chez les animaux de compagnie est souvent sub-optimale. La palatabilité d'un médicament administré par voie orale peut se révéler être un facteur déterminant dans l'amélioration de l'observance thérapeutique, tout particulièrement lorsque le médicament doit être administré quotidiennement sur une longue période. Pour leurs prescriptions thérapeutiques, les vétérinaires manquent souvent d'informations sur le caractère appétant des produits. Deux études d'appétence, l'une comprenant des tests d'acceptance et l'autre comprenant des tests de préférence, ont été conduites afin de comparer la palatabilité de formulations en comprimés appétants de deux anti-inflammatoires non stéroïdiens (AINS) – des comprimés appétants de carprofène (Rimadyl® Palatable Tablets) et des comprimés appétants de méloxicam (Metacam® Chewable Tablets for Dogs). Dans les tests d'acceptance, une consommation complète et spontanée des comprimés appétants de carprofène a été observée dans 97.8% des cas où le produit était offert, contre 13% pour les comprimés appétants de méloxicam ($P<0.0001$). Lors des tests de préférence, quand les chiens avaient le choix entre les deux produits, plus de 95% des chiens ont choisi de préférence les comprimés appétants de carprofène aux comprimés appétants de méloxicam ($P<0.0001$). En conclusion, en pratique clinique, il est raisonnable de s'attendre à ce que la prescription de comprimés appétants de carprofène entraîne une meilleure observance thérapeutique, ce qui devrait permettre d'obtenir les résultats cliniques attendus.

Mots-clés: Observance thérapeutique, palatabilité, tests d'acceptance, tests de préférence, carprofène, méloxicam, chien.

Introduction

It is generally recognised that for veterinary products for companion animals which require oral administration, compliance with the prescribed dosing regimen is often sub-optimal. Various authors have examined this issue, particularly in relation to oral antimicrobial therapy in dogs, and have demonstrated the shortcomings in owner compliance with prescribed dosing regimens [1, 2, 3]. It is reasonable to expect that owner and patient dosing compliance may also be a significant issue in relation to products for dogs whose indications are for chronic or long-term conditions and which require daily, or more frequent, oral dosing over an extended period.

Various ways of improving owner and patient compliance have been adopted and these include providing improved product information to the owner, clear and concise labelling, convenient packaging and awareness among veterinarians of the need to monitor the progress of the treatment strategy. Although "palatability" may be only one characteristic of a product likely to affect the outcome of treatment in the target species, it is recognised that it may be a highly significant factor in terms of prospective dosing compliance for drugs intended for oral administration to dogs. The value of "palatable" oral formulations which are voluntarily accepted and consumed by the dog from a bowl, or from an outstretched hand, in optimising compliance has been recognised particularly in the treatment of chronic conditions such as osteoarthrosis which require regular long term dosing [4].

In recent years, certain pharmaceutical companies have increasingly recognised the importance of the palatability of oral medications in ensuring good dosing compliance and, by association, improved clinical outcomes in small animal practice. These companies have developed new products, or enhanced the formulation of existing products, with convenience and ease of dosing in mind. This may take the form of formulations described as "chewable", "flavoured" or "palatable" and such descriptions are often incorporated in the product label.

While the registration process for veterinary drugs within Europe, and indeed globally, provides clear information relating to the safety and efficacy of the product, in general, the characteristics of the product which may affect dosing compliance may be less clearly defined. The flavour and odour associated with pharmaceutical products as perceived by the dog is a complex subject and much has been written about the approaches to achieving improved palatability of active pharmaceutical ingredients. Methods include taste masking of the active ingredient, adding food based products and adding flavours [4]. However, in most cases the precise blend of excipients and flavours used in commercial formulations is considered to be proprietary information and is not disclosed on product labelling. Thus, where a choice of products for a particular therapeutic strategy exists, there is generally no clear information available to the practising veterinarian regarding the relative palatability of the products.

It was with this objective in mind that Pfizer Animal Health sponsored the work reported in this paper which provides an evaluation of the relative palatability of commercial palatable tablet formulations of two non-steroidal anti-inflammatory drugs (NSAIDS) which are both commonly prescribed in veterinary practice for dogs, including for the treatment of osteoarthrosis. Both of the products, meloxicam and carprofen, which are manufactured by Boehringer Ingelheim Limited and Pfizer Animal Health, respectively, are licensed for use in European Countries. The therapeutic efficacy of both of these products has been demonstrated elsewhere and the tablet sizes chosen for this comparison are those commonly used for treatment of medium and large dogs.

The methodologies used to evaluate the palatability of the products have evolved from work in the pet food industry and follow those described in a recent paper which compared similar products to those under review here [5]. The strategy of using both acceptance and preference test procedures was adopted in order to provide a more comprehensive and robust evaluation of the relative palatability of the two products than would be obtained from using one or the other procedure in isolation. The data relating to the acceptance, preference for, and voluntary consumption of the products among a population of dogs of various ages and breeds should provide clear information on the relative palatability of the products and how this may influence prospective dosing compliance.

Materials and Methods

The relative palatability of tablets containing meloxicam (Metacam® Chewable Tablets for Dogs; 1.0 mg meloxicam per tablet; Boehringer Ingelheim Limited) and carprofen (Rimadyl® Palatable Tablets; 50 mg carprofen per tablet; Pfizer Animal Health) was compared in two separate studies. Both of these products are non-steroidal anti-inflammatory drugs (NSAIDs) and are licensed for veterinary use in European Countries. One of the studies used acceptance tests and the other used preference tests. In both studies, product comparisons were based on offering each dog a single dosing unit of each product (i.e. a single tablet) either separately (acceptance test procedure) or simultaneously (preference test procedure).

Consequently, depending on the bodyweight of each dog and whether the products were accepted and consumed, individual animals received dosages of meloxicam and carprofen (in mg/kg) not exceeding the respective data sheet guidelines but which did not necessarily correspond to the recommended therapeutic doses for each product.

STUDY SITE DESCRIPTION

The work described in this paper was conducted at a commercial kennel facility in The Netherlands during August 2006. The animal accommodation, standards of animal welfare, record keeping, and compliance were all appropriate to satisfy the requirements of the study protocols and local regulatory authorities. The Investigator was experienced in the study procedures and other personnel were suitably trained in order to ensure unbiased assessments of the relative palatability of the two products among the participating dogs. All dogs were individually housed in pens within a building with environmental control; the animals had exercise periods in groups or individually inside and/or outside the building.

During the study periods, all dogs had access to drinking water and were fed a commercial complete dry diet. On each study day, acceptance and preference test procedures were conducted at approximately the same time of day and on days of testing dogs were fed after completion of the test procedures.

ANIMALS

The animals selected for the two studies were dogs of various breeds and mixed breeds. The breeds represented included Basset Hound, Beagle, Belgian Shepherd, Border Collie, Boxer, Cocker Spaniel, Dalmatian, Fox Terrier, Golden Retriever, Greyhound, Pomeranian, Siberian Husky, Springer Spaniel and various unspecified mixed breeds. The details of the dogs which participated in the studies are summarised in Table I. Prior to the commencement of testing, all participating dogs were between 12 months and approximately 11 years of age and all had an estimated bodyweight of at least 12.5 kg.

All dogs had been vaccinated against canine distemper, hepatitis, parvovirus, parainfluenza and leptospirosis and had been acclimatised to their environment prior to the start of each study.

ACCEPTANCE TEST STUDY

The acceptance test study employed a two test, two day cross over design in order to compare the relative voluntary acceptance and consumption of the two products. In each acceptance test, each dog was presented with one tablet of

each of the two products independently on two separate study days (days 0 and 2). In order to reduce bias, the order in which each product was offered, i.e. a meloxicam chewable tablet (Metacam®) on day 0 and a carprofen palatable tablet (Rimadyl®) on day 2, or vice versa, was determined according to a randomised allocation plan which was designed in a way such that each product was offered to approximately 50% of the dogs on each of the two study days. Forty-six dogs participated in the study; dogs each participated in one test per day on up to two separate occasions and each product was offered to each dog once. One dog was found dead prior to testing on study day 2; the cause of death was determined to be due to a pericardial haematoma and was not considered to be associated with the study procedures and/or the product which it had partially consumed on study day 0 (meloxicam chewable tablet). The study design is summarised in Table II.

In each voluntary acceptance test, each dog was presented with one tablet of the assigned product in a bowl and the animal was given the opportunity to prehend and ingest the tablet. During preparation for each test, the two products were each handled with separate tweezers. The bowl containing the tablet was positioned on the floor inside the ani-mal's pen. A timer was started when the bowl had been positioned and the dog had been allowed access to it, and was stopped when the product entered the animal's mouth. If after 30 seconds, the tablet had not been taken into the mouth it was offered to the dog by hand. The tablet was always offered in the right hand and a further 30 seconds was allowed for the dog to prehend it. If, after a total of 60 seconds, the product had not been taken into the mouth the test was terminated. Consumption of the product, whether from the bowl or from the hand, was assessed as "full", "partial" or "none" and was recorded for each test. In this context, "full" consumption was judged to have occurred if the tablet was completely ingested; "partial" consumption was judged to have occurred if at least some but not all of the tablet was ingested; where no part of the tablet was ingested, consumption was recorded as "none". After each dog completed the test, the bowl was cleaned with kitchen paper and the operator washed his/her hands with plain water.

PREFERENCE TEST STUDY

The preference test study was designed as a paired comparison test in order to compare the relative preference for the two products. In each preference test, each dog was presented with one tablet of each of the two products (a meloxicam chewable tablet (Metacam®) and a carprofen palatable tablet (Rimadyl®)) simultaneously on three separate study days (days 0, 2 and 4) in order to assess choice and voluntary consumption. In order to reduce bias, the two products were randomly allocated to the two bowls of a test tray; one product was allocated to the left bowl and the other to the right bowl according to a randomised allocation plan. Forty-two dogs participated in the study; dogs each participated in one test per day on up to three separate occasions. One dog was withdrawn from the study after vomitus was observed on the floor of its pen and did not participate in testing on study days 2 and 4; this observation was not considered to be associated with the study procedures and/or the product which it had consumed on study day 0 (meloxicam chewable tablet). The study design is summarised in Table III.

In each preference test, each dog was presented with the test tray with one tablet of each product in each of the two bowls, according to the randomised allocation plan, and the animal was given the opportunity to prehend and ingest its choice of product. During preparation for each test, the two products were each handled with separate tweezers. The test tray was positioned on the floor inside the animal's pen. A timer was started when the test tray had been positioned and the dog had been allowed access to it, and was stopped when the first product entered the animal's mouth. If after 30 seconds, neither tablet had been taken into the mouth, both tablets were simultaneously offered to the dog by hand. The product from the left bowl of the test tray was held in the left hand and that from the right bowl in the right hand and a further 30 seconds was allowed for the dog to prehend one of the two tablets. If, after a total of 60 seconds, neither product had been taken into the mouth the test was terminated. Consumption of the product, whether from the bowl or from the hand, was assessed as "full", "partial" or "none" and was recorded for each test. In this context, "full" consumption was judged to have occurred if the tablet was completely ingested; "partial" consumption was judged to have occurred if at least some but not all of the tablet was ingested; where no part of the tablet was ingested, consumption was recorded as "none". Consumption of the second product was not permitted. After each dog completed the test, the bowls of the test tray were cleaned with kitchen paper and the operator washed his/her hands with plain water.

ANIMAL WELFARE

On each day of the studies, the general health of all of the participating animals was monitored. Any observations of abnormal health were brought to the attention of the owner of the kennels and, where appropriate, dogs received veterinary attention.

STATISTICAL ANALYSIS

For the purposes of statistical analyses, the dog was considered to be the experimental unit.

For the acceptance test study, for each dog, the outcome of the test was categorised in one of four possible ways: 1) full consumption of both products; 2) full consumption of meloxicam chewable tablets, incomplete or no consumption of carprofen palatable tablets; 3) full consumption of carprofen palatable tablets, incomplete or no consumption of meloxicam chewable tablets; 4) incomplete or no consumption of both products. The number of dogs in each of the four outcomes above was summarised and McNemar's test was used to assess any difference in full consumption of the two products at the 10% level of statistical significance.

For the preference test study, the preferred product was determined for each dog as follows: if the dog chose meloxicam chewable tablets more times than carprofen palatable tablets, it was said to have expressed a preference for meloxicam chewable tablets and *vice versa*; if the dog chose each product an equal number of times, it was said to have expressed no preference.

The number and percentage of dogs preferring each product (100*(the number of dogs preferring meloxicam chewable tablets or carprofen palatable tablets/the total number of dogs showing a preference)) was calculated and a Chi-Square test was used to compare the percentage of dogs preferring each product at the 10% level of statistical significance.

Results

There were no observations of abnormal health considered to be related to the test procedures and/or the products offered and consumed during either study.

ACCEPTANCE TEST STUDY

Over the two study days (day 0 and 2), a total of 91 individual voluntary acceptance tests were conducted. Forty-six dogs were each offered one meloxicam chewable tablet once and 45 dogs were each offered one carprofen palatable tablet once.

The results of the acceptance tests are summarised in Table IV. One of the two products was prehended in 64 out of the total of 91 individual acceptance tests. Meloxicam chewable tablets were prehended by 20 dogs (43.5% of the occasions on which they were offered) and carprofen palatable tablets were prehended by 44 dogs (97.8% of the occasions on which they were offered). For both products, the majority of dogs which actually prehended the tablet did so within the first 30 seconds of the test period; where dogs were offered a carprofen palatable tablet, 88.9% took the product from the bowl and this is illustrated in Figure 1.

The relative voluntary acceptance and consumption of the two products is illustrated in Figure 2. Of the dogs which prehended meloxicam chewable tablets, only six (13.0% of all dogs) voluntarily fully consumed the product compared with 44 dogs (97.8% of all dogs) which took and fully consumed a carprofen palatable tablet (Table IV). Statistical analysis confirmed that voluntary full consumption of the carprofen palatable tablets was significantly superior to that of the meloxicam chewable tablets ($P < 0.0001$).

	Number of dogs participating			
	Acceptance test study		Preference test study	
Breed description	Female	Male	Female	Male
Basset Hound	1		1	
Beagle	2	3	2	3
Belgian Shepherd	2		2	
Border Collie		1		
Boxer		1		1
Cocker Spaniel	3	2	3	2
Dalmatian		1		
Fox Terrier	2	1	1	1
Golden Retriever	1	1	1	1
Greyhound		1		1
Mixed breed (unspecified)	9	10	9	10
Pomeranian	1	1	1	1
Siberian Husky	1	1	1	1
Springer Spaniel		1		
Total Female/Male:	22	24	21	21
Total:	46		42	
Minimum age:	> 12 months		> 12 months	
Maximum age:	11 years		11 years	
Bodyweight:	> 12.5 kg		> 12.5 kg	

TABLE 1: Number and details of dogs participating in the studies

	Number of dogs to which products were offered	
Product	Study Day 0	Study Day 2
Meloxicam chewable tablets	23	23
Carprofen palatable tablets	23	22
Total number of dogs	46	45

TABLE 2: Study design: Acceptance test study

	Number of dogs to which products were offered		
Product	Study Day 0	Study Day 2	Study Day 4
Meloxicam chewable tablets	42	41	41
Carprofen palatable tablets			

TABLE 3: Study design: Preference test study

Product	Total number of tests	Product not prehended	Number (and percentage) of dogs Assessment of consumption where the product was prehended		
			"Full"	"Partial"	"None"
Meloxicam chewable tablets	46	26 (56.5)	6 (13.0)	3 (6.5)	11 (23.9)
Carprofen palatable tablets	45	1 (2.2)	44 (97.8)	0 (0.0)	0 (0.0)
P value			< 0.0001		

TABLE 4: Acceptance test study: Summary of the number and percentage of dogs which accepted and voluntarily consumed products

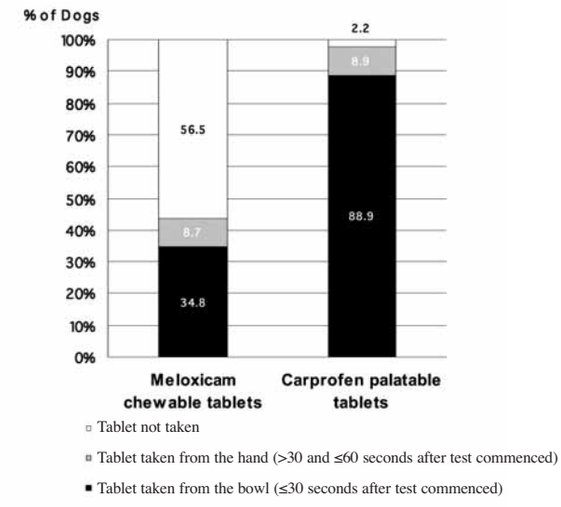

FIGURE 1: Acceptance test study: Prehension of meloxicam chewable tablets and carprofen palatable tablets

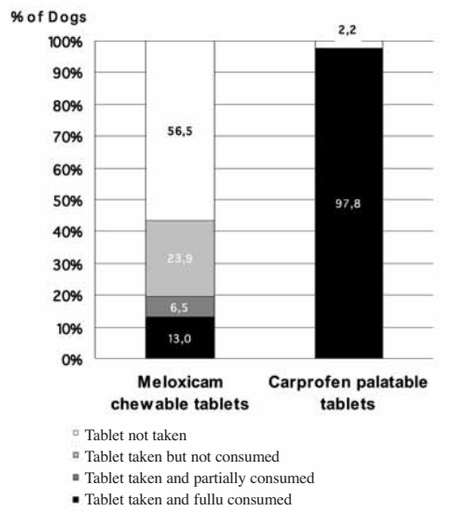

FIGURE 2: Acceptance test study: Voluntary acceptance and consumption of meloxicam chewable tablets and carprofen palatable tablets

PREFERENCE TEST STUDY

Over the three study days (days 0, 2 and 4), a total of 124 individual preference tests were conducted in which dogs were each offered one meloxicam chewable tablet and one carprofen palatable tablet simultaneously on three separate occasions (on study days 0, 2 and 4).

The results of the preference tests are summarised in Tables V and VI. One of the two products was prehended in 119 out of the total of 124 individual tests. Meloxicam chewable tablets were prehended on only six occasions (4.8% of all tests) whereas the carprofen palatable tablets were taken on 113 occasions (91.1% of all tests); on five occasions (4.0%) no choice was made (Table V). Forty-one out of the 42 dogs which participated in the study expressed a preference for one of the two products; one dog (2.4%) expressed a preference for meloxicam chewable tablets and 40 dogs (95.2%) expressed a preference for carprofen palatable tablets (Table V). Statistical analysis confirmed that the percentage of dogs preferring carprofen palatable tablets was significantly greater than for those which chose meloxicam chewable tablets ($P < 0.0001$).

When meloxicam chewable tablets were prehended, voluntary full consumption was observed on four out of six occasions (66.7%); when carprofen palatable tablets were prehended, voluntary full consumption was observed on 107 out of 113 occasions (94.7%) (Table VI).

Discussion

In both the acceptance and preference test studies, the acceptance and voluntary full consumption by dogs of the carprofen palatable tablets was high. Across the two studies, the tablets containing carprofen were prehended on more than 91% of the occasions on which they were offered. When offered a choice between the meloxicam and carprofen palatable formulations, dogs displayed a clear preference for the carprofen palatable tablets and, although meloxicam chewable tablets were accepted more readily when offered in the no choice acceptance test procedure, the acceptance of this product among this panel of dogs did not exceed 44%. Additionally, when chosen, carprofen palatable tablets were fully consumed voluntarily on more than 94% of the occasions on which they were taken into the mouth compared with the tablets containing meloxicam which were fully consumed by only 13% of dogs in the acceptance test procedure.

In both studies, where taken, carprofen palatable tablets were prehended from the bowl (i.e. within 30 seconds of the tablet being offered) on more than 88% of occasions. The evidence from both studies indicates that the tablets containing carprofen are more readily and spontaneously taken by most dogs than those containing meloxicam and these results are consistent with the high levels of acceptance and full consumption of this palatable formulation of carprofen observed in earlier work [5].

Product	Number (and percentage) of tests where a product was chosen		Number (and percentage) of individual dogs which expressed a preference	
Meloxicam chewable tablets	6	(4.8)	1	(2.4)
Carprofen palatable tablets	113	(91.1)	40	(95.2)
No choice/No preference	5	(4.0)	1	(2.4)
P value			< 0.0001	

TABLE 5: Preference test study: Summary of the number and percentage of tests where a choice was made and of the number and percentage of dogs which expressed a preference for one of the two products

Product	Total number of tests where a product was prehended	Number (and percentage) of tests Assessment of consumption where the product was prehended		
		"Full"	"Partial"	"None"
Meloxicam chewable tablets	6	4 (66.7)	0 (0.0)	2 (33.3)
Carprofen palatable tablets	113	107 (94.7)	1 (0.9)	5 (4.4)

TABLE 6: Preference test study: Summary of voluntary consumption of products where a choice was made

The acceptance and preference test procedures adopted for the product evaluation reported in this paper have evolved from methodologies used by the commercial pet food industry for testing diets in dogs and cats and have been recently used in similar product evaluations in the pharmaceutical industry. Although it is not possible, for the purposes of a controlled evaluation of two products, to accurately recreate the disparate domestic environments in which veterinary drugs are normally administered, the procedures employed for these studies used recognised methods for reducing bias and are considered to be scientifically robust and capable of producing results which are repeatable. Thus the results reported in this paper are considered to be a fair assessment of the relative palatability of the products in the mixed population of dogs at this kennel facility.

The manufacturers of both of these products have clearly made significant efforts to develop "palatable" formulations of the respective active pharmaceutical ingredients, both of which have proven therapeutic efficacy, in an attempt to enhance dosing compliance. The authors are not aware of any objective information on the flavours of carprofen and meloxicam, as perceived by dogs. Thus, without a detailed analysis of the excipients and flavours comprising both products which would have been well beyond the scope of the experimental work reported here, it is not possible to speculate on the precise reason for the significant results observed.

Conclusion

This evaluation demonstrated that carprofen palatable tablets were readily accepted and voluntarily fully consumed by a very high proportion of the mixed ages and breeds of dogs to which they were offered. When compared with meloxicam chewable tablets, carprofen palatable tablets were shown to be very significantly superior in terms of voluntary full consumption and were chosen in preference to meloxicam chewable tablets by more than 95% of dogs. Indications for both of these products include conditions which generally require long term daily dosing, thus it is a reasonable expectation that, in clinical situations, prescription of carprofen palatable tablets will ensure enhanced dosing compliance and this should assist in achieving the intended clinical outcomes.

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