Relative preference of dogs for two commercial oral tablet formulations of carprofen

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SUMMARY

A palatability study using preference tests was conducted in order to evaluate the relative preference of dogs for two commercial palatable oral tablet formulations of carprofen. Carprofen is a non-steroidal anti-inflammatory drug (NSAID) often used for management of post-operative pain and long-term therapy of osteoarthritis in dogs. In the preference tests which were conducted over three consecutive days, 65% of a panel of 60 dogs demonstrated a preference for Rimadyl® Palatable Tablets over Dolagis® tablets for dogs ($P = 0.0201$). When chosen, both products demonstrated high levels of voluntary full consumption (> 92%). In situations which require long-term daily dosing in the home environment, choosing a product which demonstrates high levels of spontaneous acceptance and ingestion is also likely to be associated with enhanced dosing compliance.

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

RÉSUMÉ

Préférence entre deux présentations commerciales de comprimés de carprofène chez le chien

Une étude d’appétence utilisant des tests de préférence a été conduite, chez le chien, afin d’évaluer la préférence relative entre deux présentations commerciales de comprimés de carprofène. Le carprofène est un anti-inflammatoire non-stéroïdien (AINS) utilisé fréquemment dans le contrôle de la douleur post-opératoire et dans le traitement à long terme de l’arthrose chez le chien. Lors des tests de préférence, qui ont été menés durant trois jours consécutifs, 65% des chiens d’un groupe de soixante ont montré une préférence pour les comprimés appétents de Rimadyl® sur les comprimés de Dolagis® ($P = 0.0201$). Lorsqu’ils étaient choisis, les deux produits ont montré des niveaux élevés de consommation volontaire (> 92%). Dans des situations nécessitant des administrations quotidiennes prolongées à la maison, le choix d’un médicament garantissant des niveaux élevés d’acceptabilité et de consommation spontanée est aussi à même de garantir une observance thérapeutique élevée.

Mots clés : Observance thérapeutique, palatabilité, tests de préférence, carprofène, chien.

Introduction

Carprofen is a non-steroidal anti-inflammatory drug (NSAID) and is widely recognised and prescribed in European countries as a safe and effective drug for analgesia and reduction of chronic inflammation, for example associated with degenerative joint disease of the dog. It is also used in the management of post-operative pain in dogs. Osteoarthritis, which is a painful and debilitating disease, usually requires long-term therapy and unlike many other conditions, treatment in the home environment by the owner is often the only practical solution. Several oral tablet formulations of carprofen are available for this purpose.

In veterinary medicine, successful treatment with any owner administered medication is dependent on both owner and patient compliance. The manner in which compliance with a prescribed treatment regime can influence the efficacy of drug therapy has been extensively studied and reviewed in a human context [5]. It is reasonable to suppose that the same factors, which include the timing of dose administration, missed doses or extended intervals between doses, will be equally relevant to therapeutic efficacy in many areas of veterinary medicine.

Animal owners administer oral tablets and capsules to dogs in a variety of ways which include offering the product by hand, placing it at the base of the tongue and encouraging the animal to swallow, concealment in food or a treat, or by crushing and sprinkling the product over food. However none of these methods work reliably for all animals at all times and oral treatment of a dog can present a considerable challenge to the owner, especially over a long course of treatment. Several authors have studied owner and patient compliance with prescribed treatment regimes. Although these studies have generally examined antimicrobial therapies, compliance with the prescribed number and timing of doses was generally found to be far from ideal and there is good reason to suppose the difficulties associated with administering oral tablets to a reluctant animal are a contributory factor to lack of compliance in all therapeutic areas [1, 2, 3, 6]. Of particular note is the finding in one study that owner compliance was significantly higher where animals were suffering from gastrointestinal infections than for animals with other conditions [6]. Thus the need for palatable oral formulations of pharmaceutical products is widely acknowledged and any formulation of a drug which is spontaneously and voluntarily consumed by most dogs will enhance patient compliance and in turn contribute to successful clinical outcomes, especially in treatment of chronic conditions where long-term dosing is necessary [10].

As the market for companion animal products has expanded, many pharmaceutical companies have recognised the com-
cmercial importance of the palatability of oral medications in ensuring good dosing compliance and have developed new products with convenience and ease of dosing in mind. This is often reflected in the product labelling by the inclusion of a description such as “chewable”, “flavoured” or “palatable”. In general, palatability is claimed where a product has been demonstrated to have a 90% or better voluntary acceptance rate in the target species [11]. Various approaches to achieving improved palatability of active pharmaceutical ingredients can be taken and these include taste masking of the active ingredient, adding food based products and/or flavours [10]. However, in general, the precise blend of excipients and flavours used in commercial formulations of pharmaceutical products is considered to be proprietary information and is not disclosed on product labelling.

Although palatability is a major consideration in drug formulation, pre-registration clinical studies focus on the safety and efficacy of new products. Thus at the time when patent protection expires and generic formulations of a medication become available it is not necessarily the case that the relative palatability of one or more products containing the same quantity of active pharmaceutical ingredient will actually be the same. Studies in dogs have demonstrated significant differences in the relative palatability of different oral tablet formulations of carprofen [8]. Without an objective evaluation of the relative palatability of different products, practising veterinarians have little or no information as to how this may affect patient compliance and, potentially, the subsequent clinical outcome.

Although there is no standard widely accepted definition of palatability, it has been suggested that in a pharmaceutical context, “palatability” can be considered to be the level of voluntary acceptance and ingestion of a product as measured by acceptance, preference or consumption tests [10]. Relative palatability may therefore be considered to be a measure of the preference a dog may express for one product over another. It is reasonable to assume that from the dog’s perspective, this is based on a subjective assessment of the appearance, odour, taste and texture of the product(s) offered. The methodologies used to evaluate the palatability of pharmaceutical products have generally evolved from work in the pet food industry where palatability is of at least equal, if not greater, importance to the manufacturer. As the subjects are unable to communicate their preferences directly, assessment of palatability must be based on an objective measure in which two or more products can be ranked on the basis of preference. Thus when designing a testing methodology it is important to eliminate as many potential sources of bias and variability as possible in order to obtain a repeatable result [7, 11, 12]. The most common method of assessing palatability employs the “two pan” test and adaptations of this preference test procedure have been successfully used to evaluate the relative palatability of various pharmaceutical products, including carprofen [8, 9].

The study reported in this paper provides an evaluation of the relative palatability of two commercial palatable tablet formulations of carprofen, Dolagis® tablets for dogs (50 mg; Laboratoires SOGEVAL) and Rimadyl® Palatable Tablets (50 mg; Pfizer Animal Health). Both products contain 50 mg carprofen per tablet. The product comparison was based on offering each dog a single dosing unit of each product (i.e. a single tablet) simultaneously in a preference test procedure. The bodyweight of dogs selected for the study was such that, in tests where one of the two products was chosen and consumed, individual animals received dosages of carprofen which did not exceed the maximum recommended dose of 4 mg/kg, as per the product data sheets. However, as all the dogs which participated in the study were healthy at the outset and the intention was not to treat, the actual doses of carprofen consumed by dogs did not necessarily correspond to the recommended therapeutic doses for either product.

STUDY SITE DESCRIPTION

The work described in this paper was conducted at a commercial kennel facility in The Netherlands during August 2008. The animal accommodation, standards of animal welfare, record keeping, and compliance were all appropriate to satisfy the requirements of the study protocol and local regulatory authorities. The Investigator was experienced in the study procedure 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 which had suitable environmental control and each animal had a daily exercise and socialisation period with other dogs either inside or outside the building. The preference test procedures commenced in the morning at approximately the same time on each of the three days of the study. Dogs were fed once daily within approximately one hour after completion of the test procedures. The daily meal comprised a maintenance allowance of a commercial complete dry dog food: Royal Canin Size Health Nutrition™ Medium Adult 25, manufactured by Royal Canin Nederland BV (average analysis as per product label: protein 25%; fat 14%; fibre 1.4%; ash 5.7%; moisture 8%; nitrogen free extract 45.9%). Uneaten food was removed before the end of the day. Throughout the study period, all dogs had access to drinking water.

ANIMALS

The dogs selected for the study were of various breeds which included Beagle, Belgian Shepherd, Border Collie, Boxer, Cocker Spaniel, Dalmatian, Fox Terrier, Golden Retriever, Greyhound, Labrador Retriever, Pomeranian, Springer Spaniel and also 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 aged between approximately one and 13 years of age and all had an estimated bodyweight of at least 12.5 kg. All dogs which participated in the study had been resident at the study site for at least two months and were acclimatised to their environment and had been vaccinated against canine distemper, hepatitis, parvovirus, parainfluenza and leptospirosis in accordance with the normal kennel procedures. On a number of occasions in the period immediately prior to the study period, all of the dogs were offered a choice of non-pharmaceutical products in the same test tray as that used for the preference tests in order to familiarise them with both the equipment and procedure.

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<tr>
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<td>- maximum:</td>
<td>13 years</td>
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<tr>
<td>Bodyweight:</td>
<td>≥ 12.5 kg</td>
</tr>
</tbody>
</table>

Table I: Description and number of dogs participating in the study

PREFERENCE TEST PROCEDURE

The study employed a preference test procedure in which each dog was presented with a single tablet of each of the two products (Dolagis® tablets for dogs (50 mg) and Rimadyl® Palatable Tablets (50 mg)) simultaneously. The test was repeated for each dog on three consecutive days and, in order to reduce bias, on each day the two products were randomly allocated to the left or right bowl of a test tray according to a randomised allocation plan. Products were stored in accordance with the manufacturer’s data sheet and during preparation for each test, tablets were removed from their packaging and handled using a separate pair of tweezers for each product in order to avoid contact with the operator’s hand.

In each preference test, each dog was presented with the test tray with one tablet of each product in each of the two bowls (left and right). The operator then positioned the test tray on the floor inside the dog’s pen and the animal was given the opportunity toprehend and ingest its choice of one of the two products. A separate person, who observed and recorded the outcome of each test, started a timer at the point when the test tray had been positioned and the dog had been allowed access to it. If after 30 seconds neither tablet had been prehended from the test tray, both tablets were then removed from the test tray and offered to the dog by hand. Both tablets were presented simultaneously in the open palm of the operator’s hands and the position of the products corresponded with their original position in the test tray (i.e. the product from the left bowl was held in the left hand and that from the right bowl in the right hand). No attempt was made to coax or persuade the dog to take either tablet. Up to a further 30 seconds was allowed for the dog to prehend one of the two tablets from the hand.

The timer was stopped when the animal first prehended one of the two products, either from the test tray or from the hand, however if neither product had been taken into the mouth after a total of 60 seconds the test was terminated. Consumption of the product, whether from the bowl or from the hand, was assessed as “full”, “partial” or “none”. 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 of the tablet was ingested; where no part of the tablet was ingested consumption was recorded as “none”. No dog was permitted to consume more than one of the two products during each test.

The testing order for the dogs was the same on each day and after each dog completed the preference test, the test tray and bowls were cleaned with kitchen paper and/or washed with plain water as required and the operator washed his/her hands with plain water.

ANIMAL WELFARE

The general health of all of the participating dogs was monitored on each day of the study and observations of abnormal health were brought to the attention of the owner of the kennels and affected animals were examined by a veterinarian.

STATISTICAL ANALYSIS

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

For each dog, the preferred product was assessed according to whether it chose one product on more occasions than the other. If the dog chose Dolagis® tablets more times than Rimadyl® tablets, it was deemed to have expressed a preference for Dolagis® and vice versa. Where the dog chose each product an equal number of times, it was deemed to have expressed no preference.

The percentage of dogs preferring each product was calculated as follows:

\[ \frac{\text{100} \times (\text{number of dogs preferring Dolagis® or Rimadyl®})}{\text{total number of dogs which expressed a preference}} \]

These percentages were compared using a two-sided Chi-Square test at the 10% level of statistical significance.
Results

A total of sixty dogs participated in the study, however two dogs which exhibited signs of abnormal health were withdrawn before completing the study. In both cases the abnormal signs were not considered to be associated with the testing procedures. As a consequence, 60 dogs participated on the first day of testing, 59 dogs participated on the second day of testing and 58 dogs participated on the third day of testing. Therefore, the results of the study are based on a total of 177 individual preference tests (see Table II).

The results of the preference tests are summarised in Tables III and IV. Out of the total of 177 individual tests, one of the two products was chosen on 172 occasions and dogs declined to make a choice on only five occasions (see Table III). In the majority of the 172 tests where a product was prehended, this occurred from one of the two bowls of the test tray i.e. within the first 30 seconds of the test period, and in only 12 tests prehension occurred in the latter 30 seconds of the test period whilst the products were being offered simultaneously in the palms of the operator’s hands. Dolagis® tablets were prehended on 69 occasions (39.0% of all tests) and Rimadyl® tablets were chosen on 103 occasions (58.2% of all tests).

All of the 60 dogs which participated in the study were deemed to have expressed a preference for one of the two products (Table III). Thirty nine dogs (65.0%) expressed a preference for Rimadyl® tablets (i.e. chose Rimadyl® on more occasions than Dolagis®) whereas only twenty-one dogs (35.0%) expressed a preference for Dolagis® tablets and this difference was found to be statistically significant (P = 0.0201).

Where Dolagis® and Rimadyl® tablets were prehended, a high level of voluntary full consumption was observed (92.8% and 94.2%, respectively) and on a relative small number of occasions dogs which had chosen one of the two products declined to fully consume it (see Table IV).

Discussion

When offered a choice between these two formulations of carprofen, 65% of the dogs which participated in the study displayed a clear preference for Rimadyl® tablets. The study also demonstrated that among this panel of dogs, the level of acceptance and full consumption of both products was high (> 92%) and on relatively few occasions (< 6%), dogs declined to fully consume the product which they had chosen.
In earlier studies involving dogs with a similar origin and background, similar high levels of acceptance and full consumption of Rimadyl® tablets were observed and dogs have expressed clear preferences for Rimadyl® tablets over other oral tablet formulations containing carprofen or other NSAIDs [8, 9]. This study provides further evidence that Rimadyl® tablets are more readily and spontaneously taken by most dogs.

No formal guidelines are currently available for evaluating the palatability of pharmaceutical products and the preference test methodology employed in the study reported in this paper has evolved from methodologies used by the commercial pet food industry for testing diets in dogs and cats. Although there can be complications in the interpretation of the results from preference tests, the methodology employed here attempted to eliminate as many of these as possible through the use of a randomised design, standardised operating procedures and diet [7, 11, 12]. Clearly, it is not possible to replicate in a laboratory or kennel environment the owner/pet interaction which occurs in the disparate domestic environments in which owner administered treatment occurs. However similar study designs have been successfully used in other recent pharmaceutical product evaluations and the methodology is considered scientifically robust and capable of producing results which are repeatable [4, 8, 9].

Both of these products are marketed as palatable formulations of the active pharmaceutical ingredient, carprofen, which has proven therapeutic efficacy and the respective manufacturers have employed unspecified flavourings to enhance the relative palatability of their products. As the animal related component of dosing compliance is clearly linked to voluntary acceptance and ingestion, it is reasonable to conclude that products which are more readily and spontaneously taken by dogs are more likely to be associated with good dosing compliance. Although this study provides no direct evidence about dosing compliance in the clinical or domestic situation the preferred product, Rimadyl® Palatable Tablets, demonstrated a high level of voluntary acceptance and full consumption in this evaluation.

Conclusion

This evaluation demonstrated that over a three day test period, when offered both products simultaneously, a panel comprising 60 dogs displayed a statistically significant preference for Rimadyl® Palatable Tablets (50 mg) over Dolagis® tablets for dogs (50 mg). In the voluntary preference test procedure 65% of dogs chose Rimadyl® tablets on more occasions than Dolagis® tablets. Both of these oral tablet formulations of carprofen are known to be clinically effective for conditions which may require long-term daily dosing and products which demonstrate high levels of spontaneous acceptance and ingestion are also likely to be associated with enhanced dosing compliance.

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References