A multicenter study of the effect of dietary supplementation with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis

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Objective—To determine the effects of feeding a diet supplemented with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis.

Design—Randomized, controlled, multisite clinical trial.

Animals—131 client-owned dogs with stable chronic osteoarthritis examined at 33 privately owned veterinary hospitals in the United States.

Procedures—In all dogs, the dosage of carprofen was standardized over a 3-week period to approximately 4.4 mg/kg/d (2 mg/lb/d), PO. Dogs were then randomly assigned to receive a food supplemented with fish oil omega-3 fatty acids or a control food with low omega-3 fatty acid content, and 3, 6, 9, and 12 weeks later, investigators made decisions regarding increasing or decreasing the carprofen dosage on the basis of investigator assessments of 5 clinical signs and owner assessments of 15 signs.

Results—Linear regression analysis indicated that over the 12-week study period, carprofen dosage decreased significantly faster among dogs fed the supplemented diet than among dogs fed the control diet. The distribution of changes in carprofen dosage for dogs in the control group was significantly different from the distribution of changes in carprofen dosage for dogs in the test group.

Conclusions and Clinical Relevance—Results suggested that in dogs with chronic osteoarthritis receiving carprofen because of signs of pain, feeding a diet supplemented with fish oil omega-3 fatty acids may allow for a reduction in carprofen dosage. (*J Am Vet Med Assoc* 2010;236:535–539)

Human clinical studies[1–6] and a recent meta-analysis[7] have found that dietary supplementation with fish oil and fish oil–derived fatty acids (in particular omega-3 fatty acids) provides benefits for patients with rheumatoid arthritis. Although the pathophysiology of rheumatoid arthritis in humans differs from the pathophysiology of OA in dogs, both conditions have an inflammatory aspect that could be sensitive to omega-3 fatty acids.[8] In 2 recent studies,[9,10] the effects of dietary supplementation with fish oil omega-3 fatty acids in dogs with OA found that feeding a diet containing 3.4% to 3.5% omega-3 fatty acids improved some clinical outcomes and weight bearing. In clinical practice, many dogs with OA are treated long term with NSAIDs such as carprofen,[11] and neither of the aforementioned studies[9,10] examined whether dietary supplementation with omega-3 fatty acids would allow a decrease in NSAID dosage. The purpose of the study reported here, therefore, was to determine the effects of feeding a diet supplemented with fish oil omega-3 fatty acids on carprofen dosage in dogs with OA.

Abbreviation

OA	Osteoarthritis

Materials and Methods

Study design and patient selection—The study was designed as a randomized, controlled, multisite clinical trial involving 33 privately owned veterinary hospitals in the United States and was conducted between August 30, 2003, and May 21, 2004. All aspects of the study were conducted in accordance with the Hill's Pet Nutrition Global Animal Welfare Policy, and the study protocol was approved by the Hill's Institutional Animal Care and Use Committee and Animal Welfare Committee. All participating owners provided written consent prior to their dogs' inclusion in the study.

Adult dogs with clinical signs and radiographic changes consistent with OA involving the hip or stifle joint that were currently receiving carprofen were considered candidates for the study. For dogs considered for inclusion in the study, investigators were required to obtain orthogonal radiographic views (eg, ventrodorsal and lateral radiographic views) and to verify the diagnosis of OA on the basis of standard criteria.[12] Dogs were enrolled if they consumed primarily a dry canine diet, were ≥ 1 year old, had a body condition score > 1 on a scale from 1 to 5 (1 = very thin, 2 = underweight, 3 = ideal, 4 = overweight, and 5 = obese), had radio-

graphic evidence of OA involving a hip or stifle joint with associated clinical signs of lameness (eg, altered gait), were currently being treated with carprofen because of the OA, and were otherwise healthy, as determined on the basis of results of a physical examination, CBC, serum biochemical panel, and urinalysis. Dogs were excluded from the study if they were participating in another clinical study or had participated in a clinical study at Hill's Pet Nutrition during the 6 months prior to the start of the present study; had any acute traumatic injuries or any conditions for which surgery was indicated (eg, fractures or chronic malunion); were receiving any medications for OA other than carprofen; were receiving corticosteroids; had undergone arthrocentesis during the 30 days prior to the start of the study; had received an intra-articular injection of any material into any joint during the 90 days prior to the start of the study or had undergone surgery on any joint during the 180 days prior to the start of the study; had any concurrent diseases involving the liver, kidneys, or gastrointestinal tract or any systemic diseases, such as lupus, borreliosis, hypothyroidism, or hyperadrenocorticism, that may have complicated evaluation of therapeutic responses; had a condition for which surgery was anticipated or planned during the feeding period; were pregnant or likely to become pregnant during the study period; or had a history of fractious behavior. Dogs were dismissed during the course of the study if they developed any adverse reactions, incurred any injuries, or developed any illnesses warranting medical or surgical treatment that prevented compliance with the study protocol or required unmasking of the experimental treatment; the investigator became unmasked; the investigator determined that the dog was unable to continue in the study because of signs of excessive pain, other complications of OA, or concurrent medical conditions; the dog owner did not comply with study restrictions or withdrew the dog from the study; or the dog was lost to follow-up, died, or was euthanatized. Finally, dogs were removed from the analysis if it was determined ex post facto that they did not meet eligibility criteria.

Study diets—Diets used in the study were the same as those used in a previous study.[10] The control diet consisted of typical adult commercial dry[a] and wet[b] formulations. The test diets consisted of dry and wet formulations of a therapeutic diet.[c] Total omega-3 fatty acid contents of the control and test diets were approximately 0.1% and 3.5%, respectively.[10] Control and test diets met or exceeded Association of American Feed Control Officials' guidelines for complete and balanced nutrition for maintenance of adult dogs.[13]

Study protocol—For dogs enrolled in the study, the dosage of carprofen[d] was standardized over a 3-week period (week −3 to week 0) to approximately 4.4 mg/kg (2 mg/lb), PO, every 24 hours or 2.2 mg/kg (1 mg/lb), PO, every 12 hours. Dosing regimen was chosen according to size of the dog, the investigator's and owner's preference, and the manufacturer's dosage chart. At week 0, dogs were randomly assigned to receive either the test or control diet. Owners were given the option of feeding their dogs the wet formulation only, the dry formulation only, or a combination of the wet and dry formulations. Owners and investigators were blinded to diet group assignment. Owners were instructed to transition dogs to the new diet over 3 to 7 days by mixing increasing amounts of the study diet with decreasing amounts of the diet the dogs had been fed prior to enrollment in the study. Feeding guidelines were provided to owners with the intent that dogs be fed according to their usual feeding regimen (free choice or meal fed) and to maintain body weight and condition. The feeding period for each dog continued for 12 weeks from the time of diet assignment (ie, from week 0 to week 12). Dogs were maintained in their owners' households during and following completion of the study.

For each dog, at weeks −3, 0, 3, 6, 9, and 12, the investigator performed a clinical evaluation of the dog, which included obtaining a complete medical history (including drug history) and performing complete physical and orthopedic examinations. A score ranging from 1 to 6 (1 = none, 2 = mild, 3 = moderate, 4 = marked, 5 = severe, and 6 = unable to assess) was assigned by the investigator to each of the following 5 items: overall arthritic condition, lameness, reluctance to bear weight, reduction in range of motion, and signs of pain on palpation of the affected joint. At the same times, a urinalysis, CBC, and serum biochemical panel, including measurement of serum fatty acids concentration, were performed. In addition, at weeks 3, 6, 9, and 12, the owner completed a questionnaire assessing the change in severity of the following 15 signs, as related to the dog's arthritic condition: difficulty in rising from rest, limping, stiffness, soreness when touched, lagging behind during walks, vocalizing in pain, aggression, difficulty in running, difficulty in walking, difficulty in stair climbing, difficulty in jumping, difficulty in playing, impaired mobility, lameness, and impaired overall activity level. Potential scores ranged from 1 to 7 (1 = dramatically improved, 2 = moderately improved, 3 = slightly improved, 4 = no difference, 5 = slightly worsened, 6 = moderately worsened, and 7 = dramatically worsened). Investigator and owner questionnaires were similar to those used in previous studies.[9,10]

Following the week 3, 6, 9, and 12 examinations, the investigator made a decision about adjusting the carprofen dosage, with the goal of maintaining the dog's condition. This decision was made on the basis of the investigator's and owner's evaluations, although the investigator was free to adjust the dosage according to his or her overall perception of the dog's condition.

During the course of the study, all adverse events were reported to the investigator, who recorded whether it was a new event, the severity of the event, whether the event was related to the study diet or concomitant medication, the nature of the event, and other relevant details. For each dog, the same veterinarian performed all clinical assessments.

Statistical analysis—A random sequence of test and control diets was generated for 20 potential patients each at 40 potential clinics by means of standard software.[e] The only restriction placed on the randomization scheme was that there had to be an equal number of test and control diets on the list for each clinic. As a dog was enrolled in the study, it was assigned to

the first available diet in the randomization sequence for the designated clinic.

Sample size was calculated with standard software[f] on the basis of an anticipated reduction in carprofen dosage of 1.1 mg/kg (0.5 mg/lb) by the end of the study for dogs receiving the test diet, SD of 1.0, α value of 0.05, and minimum power of 0.70. This calculation indicated that a minimum of 50 dogs would be required per treatment in the study. When a dismissal rate of 20% was factored in, it was decided to recruit 120 dogs for the study.

Data for carprofen dosage from all time points were analyzed by means of repeated-measures ANOVA.[g] The 33 clinics involved were considered a random effect, and the model included random effect terms for clinic and the clinic-by-treatment interaction. However, the variance component associated with the clinic-by-treatment interaction was 0; therefore, this factor was omitted from subsequent analyses.[14] To account for correlation between repeated measures, 5 common covariance models, including compound symmetry, first-order autoregressive, first-order antedependence, Toeplitz, and an unstructured model, were considered. Comparison of the Akaike information criteria for the 5 models indicated that an unstructured covariance model provided the best fit.[15] The unstructured covariance model was used to estimate separate variances for each time point and separate covariances for each pair of time points. The Kenward-Rogers procedure was used to adjust SEs and test statistics for random effects and correlated errors in the model.[15] The time main effect and the diet-by-time interaction effect were partitioned into linear, quadratic, and higher-order trends by means of orthogonal polynomial contrasts.[16] Separate linear regression models were fit to the carprofen dosage data over time for the test and control diets with standard software.[h] Slopes for the 2 regression lines were then compared by means of a t test.

Sensitivity analysis was performed with a multiple imputation procedure to examine the effects of dismissed dogs.[17] Missing data were assumed to follow a monotone missing pattern, and the Markov-chain Monte Carlo method[18] was used to impute missing values. Each missing value was replaced 10 times to generate 10 complete data sets. Each complete data set was analyzed with the same model used to analyze the incomplete data set, and results obtained were combined to provide the inferential test statistic.

The change in dosage for each dog was calculated by subtracting the dog's dosage at the end of the study (week 12) from the dog's dosage at the start of the study (week 0). Changes in carprofen dosages were assigned to 6 interval classes centered at –4.4, –3.3, –2.2, –1.1, 0, and 1.1 mg/kg (–2.0, –1.5, –1.0, –0.5, 0, and 0.5 mg/lb, respectively). Distributions of dogs among these interval classes for the test and control diets were compared by means of the Cochran-Mantel-Haenzel χ^2 test. For all analyses, a value of $P < 0.05$ was considered significant.

Results

Dogs—A total of 142 dogs were considered for inclusion in the study. Of these, 11 were excluded because they did not meet the inclusion criteria or met 1 or more exclusion criteria. Reasons for exclusion included a concurrent medical condition (n = 6), noncompliance (4), and a nontargeted form of arthritis (1).

The remaining 131 dogs were randomly assigned to receive the control (n = 66) or test (65) diet. Thirty-three clinics participated in the study, with 1 to 8 dogs enrolled/clinic. Of the 131 enrolled dogs, 22 were dismissed during the course of the study, including 9 in the control group and 13 in the test group. One dog in the control group was dismissed because of a concurrent condition (dismissed on day 38), 2 were dismissed because of lack of owner compliance (days 30 and 39),

Table 1—Characteristics of dogs with OA fed a diet supplemented with fish oil omega-3 fatty acids (n = 52) or a control diet with standard omega-3 fatty acids content (57) in a study designed to assess the effect of dietary supplementation with omega-3 fatty acids on carprofen dosage in dogs with OA.

Characteristic	Control diet	Test diet	P value
Age at study enrollment (y)	8.9 ± 0.4 (2 to 15)	8.8 ± 0.5 (2 to 15)	0.85
Weight (kg)			
Week 0	30.2 ± 1.5 (3.6 to 50.3)	32.1 ± 1.9 (3.6 to 65.8)	0.41
Week 12	30.6 ± 1.5 (3.6 to 50.3)	32.4 ± 1.9 (3.6 to 63.0)	0.45
Change	0.39 ± 0.21 (–3.6 to 5.0)	0.24 ± 0.23 (–3.2 to 5.0)	0.62
Body condition score			
Week 0	3.54 ± 0.09 (2 to 5)	3.56 ± 0.10 (2 to 5)	0.91
Week 12	3.58 ± 0.09 (2 to 5)	3.46 ± 0.10 (2 to 5)	0.38
Change	0.04 ± 0.08 (–1 to 1)	–0.10 ± 0.06 (–1 to 1)	0.19
Sex			0.40
Female	32 (56)	25 (48)	
Male	25 (44)	27 (52)	
Reproductive status			0.89
Sexually intact	4 (7)	4 (8)	
Neutered	53 (93)	48 (92)	
Primary affected joint at study enrollment			0.56
Stifle (single joint)	5 (9)	7 (13)	
Stifle (multiple joints)	11 (19)	7 (13)	
Hip (single joint)	15 (26)	18 (35)	
Hip (multiple joints)	26 (46)	20 (38)	

Data are given as mean ± SD (range) or as number of dogs (percentage).

Table 2—Daily carprofen dosage (mg/kg/d) in dogs with OA fed a diet supplemented with fish oil omega-3 fatty acids (n = 52) or a control diet with standard omega-3 fatty acids content (57).

Week	Diet	Mean ± SE	Median	Range
0	Control	4.17 ± 0.09	4.16	2.19–6.42
	Test	4.39 ± 0.10	4.40	3.15–6.80
3	Control	4.16 ± 0.12	4.22	2.01–6.13
	Test	4.21 ± 0.12	4.35	1.72–6.80
6	Control	3.74 ± 0.14	3.85	1.87–6.13
	Test	3.86 ± 0.15	4.04	1.07–6.80
9	Control	3.63 ± 0.16	3.89	0.94–6.13
	Test	3.42 ± 0.16	3.63	0.84–6.80
12	Control	3.58 ± 0.16	3.85	0.94–6.16
	Test	3.26 ± 0.17	3.52	0.54–5.22

Dogs were examined every 3 weeks, and carprofen dosage was adjusted by the attending veterinarian on the basis of veterinarian and owner assessments of OA severity. During the 3 weeks prior to week 0, carprofen dosage was adjusted in all dogs to approximately 4.4 mg/kg/d. To convert dosages in mg/kg/d to dosages in mg/lb/d, divide by 2.2.
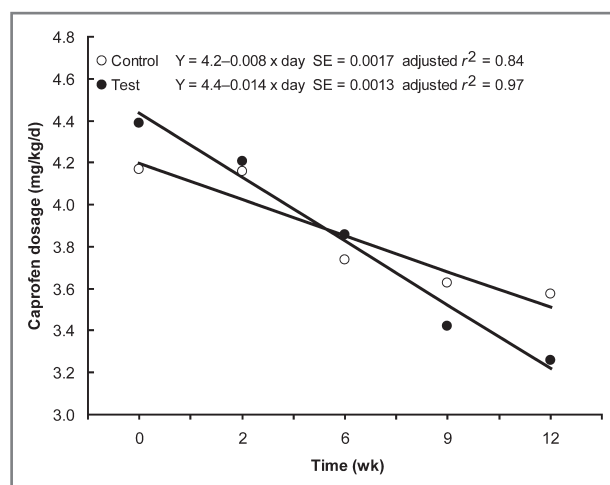

Figure 1—Mean daily carprofen dosage in dogs with OA fed a diet supplemented with fish oil omega-3 fatty acids (n = 52) or a control diet with standard omega-3 fatty acids content (57). Dogs were examined every 3 weeks, and carprofen dosage was adjusted by the attending veterinarian on the basis of veterinarian and owner assessments of OA severity. Solid lines represent results of least squares linear regression analysis. Slopes of the lines were significantly (P = 0.025) different.
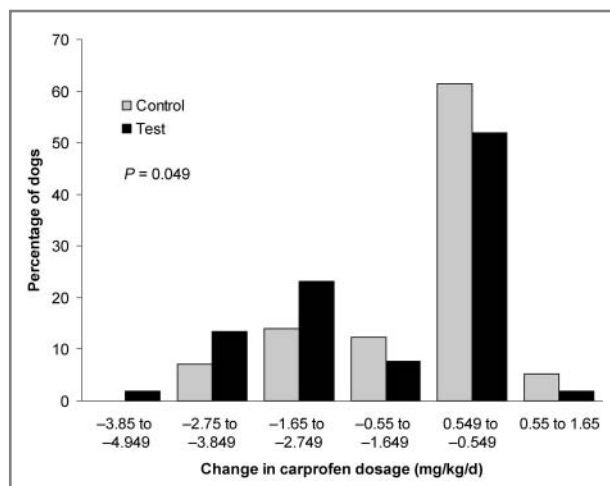

Figure 2—Distribution of changes in carprofen dosage (ie, week 12 dosage minus week 0 dosage) for the dogs in Figure 1. Distribution of changes in carprofen dosage was significantly (P = 0.049) different between groups.

1 was euthanatized (day 79), 3 were dismissed because of an adverse event (days 5, 31, and 37), 1 was dismissed because of poor food palatability (day 22), and 1 was dismissed because of deterioration in the arthritic condition (day 66). Four dogs in the test group were dismissed because of a concurrent condition (days 5, 13, 25, and 26), 4 were dismissed because of lack of owner compliance (days 40, 45, 50, and 106), 2 were euthanatized (days 19 and 97), 2 were dismissed because of poor food palatability (days 22 and 40), and 1 was dismissed because of deterioration in the arthritic condition (day 40).

A total of 109 dogs completed the study, including 57 in the control group and 52 in the test group. There were no significant differences between groups in regard to baseline (week 0) age, body weight, or body condition score or in regard to distribution of involved joint, sex distribution, or distribution of reproductive status (**Table 1**). There was also no significant difference in veterinarian-assessed overall arthritic condition between the groups at baseline.

Adjustments in carprofen dosage—For dogs that completed the study, carprofen dosage at the time of assignment to diet groups (ie, week 0) ranged from 2.19 to 6.42 mg/kg/d (0.99 to 2.91 mg/lb/d) for dogs in the control group and from 3.15 to 6.80 mg/kg/d (1.43 to 3.09 mg/lb/d) for dogs in the test group (**Table 2**). When carprofen dosage at week 12 was compared with dosage at week 0, 35 of the 57 (61%) dogs in the control group had no change in dosage, 3 (5%) had an increase in dosage, and 19 (33%) had a decrease in dosage. By contrast, 27 of the 52 (52%) dogs in the test group had no change in dosage, 1 (2%) had an increase in dosage, and 24 (46%) had a decrease in dosage.

Analysis of data for carprofen dosage revealed a significant (P = 0.044) day-by-diet interaction, indicating that the 2 diets had significantly different effects over the course of the study that were attributable to a significantly (P = 0.025) more rapid decrease in carprofen dosage for dogs in the test group, compared with the decrease in dosage for dogs in the control group (**Figure 1**). We did not detect significant effects of prestudy dosage adjustments, administration frequency (once vs twice daily), time of carprofen administration, or body weight of the dog at the beginning of the study on the difference between the control and test groups. Sensitivity analysis involving data for the 22 dogs dismissed from the study revealed a significant (P = 0.027) linear diet-by-time interaction, indicating that inclusion of dogs dismissed from the study would not have altered the finding of a significant difference between the 2 groups.

The distribution of changes in carprofen dosage for dogs in the control group was significantly (P = 0.049) different from the distribution of changes in carprofen dosage for dogs in the test group (**Figure 2**). Evaluation of the distributions suggested that results were not skewed by extreme values.

Discussion

Results of the present study suggested that in dogs with chronic OA receiving carprofen because of signs of pain, feeding a diet supplemented with fish oil omega-3 fatty acids may allow for a more rapid reduction in carpro-

fen dosage, compared with feeding a control diet. Specifically, dogs in the test group had a significantly more rapid decrease in carprofen dosage over the 12-week study period, compared with the decrease in carprofen dosage for dogs in the control group. In addition, the distribution of changes in carprofen dosage between week 12 and week 0 differed significantly between the 2 groups.

The present study included a 3-week period prior to assignment to diet groups during which carprofen dosage in enrolled dogs was adjusted to a standard dosage. We considered it possible that an increase in dosage during this period, compared with the dosage prescribed by the primary care veterinarian prior to study enrollment, could have accounted in part for the reduction in carprofen dosage over time in the 2 groups. Although this may have occurred, the statistical analysis indicated that changes in dosage during this adjustment period did not affect the relative difference between effects of the 2 diets. Reductions in carprofen dosage in both groups may also have been attributable, in part, to a bias toward decreasing carprofen dosage because of knowledge that dogs were participating in a clinical study for which this was a goal.

Each investigator in the present study used his or her own criteria to determine the severity of clinical signs of OA and therefore to determine whether the dosage of carprofen could be changed. This could have resulted in heterogeneity among participating veterinary clinics related to, for example, differences in skills and training of the participating veterinarians, severity of OA at participating clinics, the way the assessments were done, or the standard of care. In fact, we found that there were significant site-to-site variations in the absolute dosage of carprofen; however, heterogeneity among sites did not significantly affect the relative difference between effects of the 2 diets.

The reductions in carprofen dosage found in the present study may help minimize the possibility of adverse effects associated with long-term use. It is possible that the supplemented diet enhanced the effect of carprofen indirectly by, for example, altering drug bioavailability. However, because the pharmacokinetics of carprofen are not affected by food intake,[19] alteration of the bioavailability of carprofen was probably not the principal reason for the effects of the supplemented diet in the present study. Finally, results of the present study agree well with findings of 2 previous studies,[9,10] which showed that dietary supplementation with fish oil omega-3 fatty acids can help reduce the severity of OA, although further studies are needed to assess the long-term effects of fish oil omega-3 fatty acids in the treatment of this disease.

a.   Purina Dog Chow, Nestlé Purina PetCare Co, St Louis, Mo.
b.   Pedigree Choice Cuts, Mars Petcare US, Brentwood, Tenn.
c.   Prescription Diet j/d Canine, Hill's Pet Nutrition Inc, Topeka, Kan.
d.   Rimadyl, Pfizer Animal Health, New York, NY.
e.   PROC PLAN, SAS, version 9.1.3, SAS Institute Inc, Cary, NC.
f.   PROC POWER, SAS, version 9.1.3, SAS Institute Inc, Cary, NC.
g.   PROC MIXED, SAS, version 9.1.3, SAS Institute Inc, Cary, NC.
h.   PROC REG, SAS, version 9.1.3, SAS Institute Inc, Cary, NC.

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