Effects of meloxicam on severity of lameness and other clinical signs of osteoarthritis in dogs

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Objective—To evaluate effects of meloxicam on severity of lameness and other clinical signs in dogs with osteoarthritis (OA).

Design—Randomized, controlled, multicenter clinical trial.

Animals—217 client-owned dogs with clinical and radiographic signs of OA.

Procedure—Dogs were randomly assigned to be treated with meloxicam (n = 105; 0.2 mg/kg [0.09 mg/lb], SC, once on day 1, then 0.1 mg/kg [0.045 mg/lb], PO, q 24 h, for 13 days) or a placebo (n = 112). A general clinical score was assigned by investigators on days 1 (ie, prior to initiation of treatment), 8, and 15 on the basis of severity of lameness, extent of weight bearing, and severity of signs during palpation of the affected joint. Owners and investigators provided overall evaluations on days 8 and 15.

Results—Dogs treated with meloxicam had significantly greater improvements in general clinical scores, compared with baseline scores, on days 8 and 15 than did dogs treated with placebo. On days 8 and 15, percentages of dogs treated with meloxicam in which owners and investigators considered treatment to be successful were significantly higher than percentages of control dogs in which treatment was considered to be successful. No abnormalities in hematologic and serum biochemical test results were detected.

Conclusions and Clinical Relevance—Results suggest that compared with administration of a placebo, administration of meloxicam for 14 days significantly improved the clinical condition of dogs with OA without causing adverse effects. (*J Am Vet Med Assoc* 2004;225:1056–1060)

Meloxicam is a nonsteroidal anti-inflammatory drug of the oxicam class. It is well absorbed following oral administration, and its absorption is not affected by food.[1-3] It has an elimination half-life of approximately 24 hours, which allows for once a day administration.[1,2] In vivo and in vitro data indicate that meloxicam selectively inhibits cyclooxygenase-2 activity, while sparing cyclooxygenase-1 activity.[4-8] These findings are consistent with the reported low incidence of adverse gastrointestinal tract effects in clinical trials of meloxicam in dogs.[9-11]

Several clinical studies[9,10,12-16] have provided subjective and objective data documenting meloxicam's efficacy in treating acute and chronic pain in dogs and cats. However, only 2 of these studies[9,10] specifically evaluated meloxicam's effects in dogs with chronic **osteoarthritis (OA)** in a blinded randomized fashion, and both studies used small populations (< 20 dogs/group). Thus, there is a paucity of data about the clinical efficacy of meloxicam in dogs with signs related to chronic OA. Therefore, the purpose of the study reported here was to evaluate the effectiveness of meloxicam on severity of lameness and other clinical signs in dogs with OA. The study was designed as a multicenter, prospective, randomized, controlled clinical trial. The hypothesis tested was that meloxicam would improve the function of dogs with clinical signs of OA to a greater extent than would a placebo.

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Materials and Methods

Study design—The study was designed as a randomized, controlled, multicenter clinical trial. Investigators at 21 study sites throughout the United States enrolled dogs in the study. The study goal was to enroll at least 200 dogs in the study, with a mean of 10 dogs enrolled at each study site. Owners of all dogs enrolled in the study provided written confirmation of informed consent.

Selection criteria—Privately owned dogs > 9 months old that were overtly healthy other than having signs of OA involving the shoulder, elbow, carpal, hip, stifle, or tarsal joint were eligible for inclusion in the study. Specifically, dogs must have had at least 2 of the following signs: signs of pain during palpation of the affected joint, unwillingness to use the affected joint, swelling of the affected joint, perceptible heat involving the skin over the affected joint, crepitus of the affected joint, and stiffness of the affected joint. Dogs with bilateral OA or with multiple joint involvement (eg, concomitant shoulder and elbow OA) were eligible for inclusion in the study; however, in each dog, a single joint considered by the investigator as the most severely affected was designated as the affected joint. Dogs were included in the study only if the diagnosis of OA was confirmed radiographically.

For dogs that had previously received medical treatment for OA, an appropriate washout period (14 days for dogs that had received corticosteroids topically or systemically and for dogs that had received nonsteroidal anti-inflammatory drugs and 1 month for dogs that had received glycosaminoglycan-containing products or long-acting corticosteroid preparations) was required prior to enrollment in the study. Dogs with muscular weakness secondary to an endocrine or metabolic disease (eg, electrolyte abnormalities, hypothyroidism, hypoadrenocortism, or hyperadrenocortism) were excluded from the study, as were dogs with a history of blood dyscrasia; dogs with hepatic, renal, or cardiac disease; dogs that were pregnant or lactating; dogs with a grade 3 or higher (on a scale from 1 to 6) cardiac murmur and exercise intolerance; dogs with lameness associated with neoplasia; and dogs with a primary neurologic disorder.

Study protocol—Dogs that met the criteria for inclusion in the study underwent an initial evaluation consisting of a

physical examination, CBC, serum biochemical profile, and urinalysis. In addition, scores were assigned on the basis of severity of lameness. A modification of a previously described lameness scoring system was used.[17] Briefly, a lameness score of 1 was assigned if the dog stood and walked normally, a score of 2 was assigned if the dog stood normally with slight lameness when walking, a score of 3 was assigned if the dog stood normally with obvious lameness when walking, a score of 4 was assigned if the dog had an abnormal stance with slight lameness when walking, and a score of 5 was assigned if the dog had an abnormal stance with obvious lameness when walking. For weight bearing, a score of 1 was assigned if the dog bore weight normally on all limbs at rest and when walking, a score of 2 was assigned if the dog bore weight normally at rest and would bear partial weight on the affected limb when walking, a score of 3 was assigned if the dog would bear only partial weight at rest and when walking, a score of 4 was assigned if the dog would bear only partial weight at rest and would not bear weight when walking, and a score of 5 was assigned if the dog would not bear weight on the affected limb at rest or when walking. Scores for signs of pain during and resistance to manipulation of the affected joint were assigned, with a score of 1 assigned if the dog had no detectable response to manipulation of the limb, a score of 2 assigned if the dog had a mild response to manipulation (eg, turned its head toward the limb), a score of 3 assigned if the dog had a moderate response to manipulation (eg, the dog withdrew the limb), and a score of 4 assigned if the dog had severe response to manipulation (eg, the dog vocalized or became aggressive). A **general clinical score (GCS)** was then calculated by summing individual scores for severity of lameness, extent of weight bearing, and signs of pain during manipulation of the affected joint. Potential scores ranged from 3 to 14.

Following this initial evaluation, dogs were randomly assigned in blocks of 4 to treatment (meloxicam) and control (placebo) groups. Randomization was carried out separately at each of the 21 study sites; randomization in blocks of 4 was used to maintain balance in the study groups. Three randomization sheets were prepared for each study site: 1 for small dogs (ie, dogs weighing < 7 kg [15.4 lb]), 1 for medium dogs (ie, dogs weighing between 7 and 34 kg [15.4 and 74.8 lb]), and 1 for large dogs (ie, dogs weighing > 34 kg [74.8 lb]). Sex of the dog was not considered a blocking factor in the randomization procedure. Both the investigators and owners were masked to treatment assignment.

Dogs in the treatment group were treated with meloxicam[a] at a dose of 0.2 mg/kg (0.09 mg/lb), SC, once on the first day (day 1), followed by 0.1 mg/kg (0.045 mg/lb), PO, once a day for 13 days (days 2 through 14). Dogs in the control group were treated in an identical manner with a placebo that was identical other than not containing meloxicam. All other treatments that might affect clinical signs of OA (eg, other anti-inflammatory drugs) were prohibited throughout the study. However, treatments that were not known to have any effect on the treatment of OA (eg, heartworm preventatives) were permitted.

Dogs could be removed from the study if the investigator determined that an illness, injury, complication, or adverse reaction prohibited the dog from completing the study. In addition, dogs with a BUN concentration > 33 mg/dL or serum creatinine concentration > 2.2 mg/dL on day 1 or 8 were removed from the study. Owners were able to withdraw their dogs from the study at any time.

Evaluation of treatment efficacy—Dogs were reexamined on days 8 (ie, day 7, 8, or 9) and 15 (ie, day 14, 15, or 16). A physical examination, CBC, serum biochemical profile, and urinalysis were performed, and a GCS was assigned. An overall assessment of the response to treatment was assigned by the investigator (excellent = clinical signs resolved, good = clinical signs clearly improved, fair = minimal clinical improvement, poor = no clinical response to treatment or signs had worsened). In addition, the owner was asked to provide an assessment of the relative improvement in the dog's condition (greatly improved, moderately improved, slightly improved, or not improved). At each location, a single investigator performed all clinical assessments for each dog.

Statistical analyses—Data for study sites that failed to enroll at least 2 dogs in each treatment group were eliminated from all analyses except for evaluation of hematologic and serum biochemical results. General clinical scores obtained on days 1 (baseline), 8, and 15 and the change in GCSs over time were analyzed by use of mixed-model ANOVA with treatment incorporated as a fixed effect and study site incorporated as a random effect. A treatment by study site interaction was initially included in the model but was dropped because it did not have a significant effect on outcome. Scores for each of the 3 components of the GCS (ie, severity of lameness, extent of weight bearing, and signs of pain during manipulation of the affected joint) and changes in scores were analyzed in the same manner. Confidence intervals for the mean difference between treatments were calculated on the basis of appropriate variance estimates from the ANOVA. The assumption that data were normally distributed was verified by applying the Wilk-Shapiro test to residuals from each ANOVA.

Data on investigator- and owner-provided qualitative assessments on days 8 and 15 were analyzed by means of multiple logistic regression analysis incorporating terms for treatment, study site, and the treatment by study site interaction. For these analyses, responses were dichotomized as treatment success or failure. For the investigator-provided assessments, responses of excellent and good were considered indicative of treatment success and responses of fair and poor were considered indicative of treatment failure. For the owner-provided assessments, responses of greatly or moderately improved were considered indicative of treatment success and responses of slightly or not improved were considered indicative of treatment failure. Confidence intervals for the percentages of dogs in which treatment was successful were calculated on the basis of the estimated coefficients of the fitted multiple logistic regression model. For all analyses, values of $P \leq 0.05$ were considered significant.

Results

A total of 224 dogs were enrolled in the study; however, 3 of the 21 study sites failed to enroll the required minimum of 2 dogs in each treatment group, and data for the 6 dogs (3 assigned to the meloxicam group and 3 assigned to the placebo group) enrolled at these 3 sites were eliminated from analyses. In addition, 1 dog developed an adverse reaction after receiving the first dose of medication and was removed from the study, even though the investigator believed that the adverse reaction was unrelated to the treatment. As a result, data for 217 dogs, of which 105 were assigned to the meloxicam group and 112 were assigned to the placebo group, were included in the study.

Mean ± SD age of the 105 dogs assigned to the meloxicam group was 8.2 ± 3.2 years (range, 1.3 to 14.0 years), and mean body weight was 31.7 ± 12.6 kg (69.6 ± 27.8 lb; range, 3.9 to 66.4 kg [8.5 to 146 lb]). Mean age of the 112 dogs assigned to the control group was 8.2 ± 3.6 years (range, 1.0 to 14.0 years), and mean body weight was 30.6 ± 14.8 kg (67.4 ± 32.5 lb; range,

3.5 to 77.0 kg [7.6 to 169.3 lb]). Stiffness, signs of pain during manipulation of the affected joint, crepitus, and an unwillingness to use the affected joint were the most common clinical signs and were seen in 99 (94%), 82 (78%), 65 (62%), and 57 (54%), respectively, dogs in the meloxicam group and 104 (93%), 89 (79%), 66 (59%), and 69 (62%), respectively, dogs in the placebo group. Swelling of the affected joint was seen in 32 (30%) dogs in the meloxicam group and 33 (29%) dogs in the placebo group. Perceptible heat involving the skin overlying the affected joint was seen in only 10 (10%) dogs in the meloxicam group and 4 (4%) dogs in the placebo group. For dogs in the meloxicam group, affected joints included the hip joint (43 [41%]), stifle joint (37 [35%]), elbow joint (17 [16%]), shoulder joint (3 [3%]), tarsal joint (3 [3%]), and carpal joint (2 [2%]). For dogs in the placebo group, affected joints included the hip joint (50 [45%]), stifle joint (28 [25%]), elbow joint (23 [21%]), shoulder joint (6 [5%]), tarsal joint (2 [2%]), and carpal joint (3 [3%]).

One dog (assigned to the meloxicam group) was removed from the study after day 8 because of a deviation from the inclusion criteria. The dog was inadvertently enrolled in the study even though it had a high BUN concentration (39 mg/dL) on day 1. When the BUN concentration was still found to be high on day 8 (41 mg/dL), the dog was removed from the study. Three other dogs (1 assigned to the meloxicam group and 2 assigned to the placebo group) were removed from the study after day 8 but before day 15 because of adverse reactions. Data collected from these 4 dogs prior to their removal from the study were included in analyses. Thus, for baseline and day 8 analyses, data for 217 dogs (105 assigned to the meloxicam group and 112 assigned to the placebo group) were included, but for day 15 analyses, data for 213 dogs (103 assigned to the meloxicam group and 110 assigned to the placebo group) were included.

Mean baseline (day 1) GCSs were not significantly different between meloxicam-treated and control groups (7.4 and 7.2, respectively; **Table 1**). On both days 8 and 15, mean improvement in GCS (ie, mean change from baseline GCS) for meloxicam-treated dogs (2.0 and 2.5, respectively) was significantly greater than the mean improvement for control dogs (1.2 and 1.5, respectively).

Results of analyses for the 3 components of the GCS (ie, scores for severity of lameness, extent of weight bearing, and signs of pain during manipulation of the affected joint) were similar to results of analyses of GCSs (Table 1). In particular, mean improvements in scores for severity of lameness and extent of weight bearing were significantly greater for meloxicam-treated than for control dogs on days 8 and 15. Mean improvement in score for signs of pain during manipulation of the affected joint was significantly greater for meloxicam-treated than for control dogs on day 8 but not on day 15.

On days 8 and 15, percentage of dogs in the meloxicam group for which investigators considered

Table 1—Mean ± SEM clinical scores for dogs with osteoarthritis treated with meloxicam (n = 105; 0.2 mg/kg [0.09 mg/lb], SC, once on day 1, then 0.1 mg/kg [0.045 mg/lb], PO, q 24 h, for 13 days) or a placebo (n = 112).

		GCS		Change in GCS from baseline		
Score	**Day**	**Meloxicam**	**Placebo**	**Meloxicam**	**Placebo**	***P* value**
GCS						
	1 (baseline)	7.4 ± 0.3	7.2 ± 0.3	NA	NA	NA
	8	5.5 ± 0.3	6.0 ± 0.3	2.0 ± 0.2	1.2 ± 0.2	0.004
	15	5.1 ± 0.3	5.8 ± 0.3	2.5 ± 0.2	1.5 ± 0.2	0.003
Severity of lameness score						
	1 (baseline)	2.9 ± 0.1	2.7 ± 0.1	NA	NA	NA
	8	2.0 ± 0.1	2.2 ± 0.1	0.8 ± 0.1	0.5 ± 0.1	0.013
	15	1.8 ± 0.1	2.1 ± 0.1	1.1 ± 0.1	0.6 ± 0.1	0.005
Extent of weight bearing score						
	1 (baseline)	2.2 ± 0.1	2.1 ± 0.1	NA	NA	NA
	8	1.7 ± 0.1	1.9 ± 0.1	0.5 ± 0.1	0.3 ± 0.1	0.024
	15	1.5 ± 0.1	1.8 ± 0.1	0.7 ± 0.1	0.4 ± 0.1	0.013
Signs of pain during joint manipulation score						
	1 (baseline)	2.4 ± 0.1	2.3 ± 0.1	NA	NA	NA
	8	1.8 ± 0.1	1.9 ± 0.1	0.7 ± 0.1	0.4 ± 0.1	0.022
	15	1.7 ± 0.1	1.9 ± 0.1	0.7 ± 0.1	0.5 ± 0.1	0.063

GCS = General clinical score. NA = Not applicable.

General clinical score was calculated as the sum of scores for severity of lameness (1 = stands and walks normally, 2 = stands normally with slight lameness when walking, 3 = stands normally with obvious lameness when walking, 4 = abnormal stance with slight lameness when walking, 5 = abnormal stance with obvious lameness when walking), extent of weight bearing (1 = normal weight bearing on all limbs at rest and when walking, 2 = normal weight bearing at rest and partial weight bearing when walking, 3 = partial weight bearing at rest and when walking, 4 = partial weight bearing at rest and non-weight bearing when walking, 5 = non-weight bearing at rest and when walking), and signs of pain during and resistance to manipulation of the affected joint (1 = no response detectable to manipulation of the limb; 2 = mild response to manipulation, turns head toward limb; 3 = moderate response to manipulation, withdraws limb; 4 = severe pain response to manipulation, vocalizes or becomes aggressive).

Table 2—Investigator- and owner-based assessments of treatment success rates for dogs with osteoarthritis treated with meloxicam for 14 days or a placebo.

Assessment	Day	Meloxicam	Placebo	*P* value
Investigator				
	8	48 (34–62)	29 (18–42)	0.053
	15	63 (52–72)	38 (29–49)	0.001
Owner				
	8	51 (40–62)	28 (19–38)	0.005
	15	62 (52–72)	32 (23–42)	< 0.001

Data are given as percentage (95% confidence interval).

Investigators provided an overall assessment of the response to treatment (excellent = clinical signs resolved, good = clinical signs clearly improved, fair = minimal clinical improvement, poor = no clinical response to treatment or signs had worsened), with treatment considered successful in dogs with an excellent or good response to treatment. Owners provided an assessment of the relative improvement in the dog's condition (greatly improved, moderately improved, slightly improved, or not improved), with treatment considered successful in dogs that were greatly or moderately improved.

treatment to be successful (ie, excellent or good response to treatment) was significantly higher than percentage of dogs in the placebo group for which investigators considered treatment to be successful (**Table 2**). Similarly, percentage of dogs in the meloxicam group for which owners considered treatment to be successful (ie, greatly or moderately improved) was significantly higher than percentage of dogs in the placebo group.

Hematological and serum biochemical test results demonstrated no abnormalities or clinically relevant changes over the course of the study.

Discussion

Results of the present study suggest that compared with a placebo, administration of meloxicam for 14 days significantly improved the clinical condition of dogs with OA without causing adverse effects. This is consistent with results of other clinical and research studies[9,10,12,14-19] of the effects of meloxicam in dogs.

In the present study, we used a subjective score (ie, the GCS) that involved assessments of the severity of lameness, extent of weight bearing, and signs of pain elicited during manipulation of the affected joint as a means of evaluating clinical condition of the dogs and changes in clinical condition over time. Our ability to detect significant differences between groups suggests that certain subjective scoring systems can be effective tools in discriminating the severity of pain and dysfunction caused by OA in dogs. This is similar to results of a previous study[20] but contrasts with results of other studies[21,22,b] in which subjective evaluations were insensitive to differences between treatment and control groups. One potential explanation for this difference is the large number of dogs included in the present study. This large sample size increased the power of the study and reduced the potential for type II errors.

As in the present study, several previous studies[9,10,12,21,22] have used general or global scoring systems for veterinarians and owners to assess the efficacy of treatment in dogs with OA. This is consistent with the use of physician- and patient-based outcome measurements in human studies.[23-26] Assessments of overall improvement from investigators and owners in the present study were largely as expected. The percentages of dogs in the placebo group for which investigators and owners considered treatment to be successful (29% and 28%, respectively, on day 8 and 38% and 32%, respectively, on day 15) demonstrated the importance of the placebo effect and emphasized the need for randomized controlled trials when evaluating the effect of anti-inflammatory drugs in dogs. Investigator and owner assessments of treatment success rates were similar in the present study, which agrees with findings in a study[10] of the treatment of chronic OA in dogs. However, our findings are in contrast to findings in 2 studies[21,22] in which owner observations were more sensitive than observations by attending veterinarians at discerning placebo from treatment during management of pain in dogs. It has been postulated that combining scores from veterinarian and owner assessments into an index score may provide greater accuracy for assessing chronic pain in dogs.[22,27]

In the present study, no abnormalities in hematologic or serum biochemical test results were detected. These data are consistent with results of previous studies[9,10,12,14] and suggest that administration of meloxicam is safe, at least during the time frames of these studies.

[a]Metacam, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.

[b]Johnston SA, Conzemius MG, Cross AR, et al. A multi-center clinical study of the effect of deracoxib a COX-2 selective drug on chronic pain in dogs with osteoarthritis (abstr). *Vet Surg* 2001;30:497.

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