Clinical efficacy and tolerance of meloxicam in dogs with chronic osteoarthritis

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Abstract — A clinical trial was conducted to evaluate the safety and efficacy of the nonsteroidal anti-inflammatory drug meloxicam in dogs with chronic osteoarthritis. Forty clinical cases were enrolled in the 2-phase study. Phase 1 compared therapeutic efficacy and tolerance of meloxicam or placebo for 1 week. Phase 2 involved a 4-week evaluation of the drug's clinical efficacy and tolerance. Clinical efficacy was evaluated by using a scoring system that assessed specific lameness, general stiffness, painful rise, exercise intolerance, and behavior. Evaluations demonstrated significant reductions ($P < 0.05$) in clinical signs of osteoarthritis following 4 weeks of drug therapy. Side effects were minimal in extent and duration. The drug was accepted without problems in the majority of cases. The findings of this investigation suggest that the efficacy, tolerance, and formulation of meloxicam oral suspension make it well suited for the treatment of chronic osteoarthritis in the dog.

Résumé — Efficacité clinique et tolérance au méloxicam chez des chiens atteints d'ostéoarthrite chronique. Une étude clinique a été effectuée afin d'évaluer la sécurité et l'efficacité du méloxicam, un anti-inflammatoire non-stéroïdien, chez des chiens présentant une ostéoarthrite chronique. Quarante cas cliniques ont été inclus dans cette étude en 2 phases. Dans la phase 1, qui s'étendait sur 1 semaine, le méloxicam et le placebo ont été comparés aux points de vue de l'efficacité thérapeutique et de la tolérance. La phase 2 impliquait une évaluation du médicament par rapport à l'efficacité clinique et la tolérance pendant une période de 4 semaines. L'efficacité clinique a été évaluée par un système de cotation qui évaluait la boiterie spécifique, la raideur générale, le levé douloureux, l'intolérance à l'exercice et le comportement. Les évaluations ont démontré une réduction significative ($P < 0,05$) des signes cliniques de l'ostéoarthrite après 4 semaines de thérapie médicamenteuse. L'importance et la durée des effets secondaires étaient minimes. Le médicament a été accepté sans problèmes dans la majorité des cas. Les résultats de cette étude suggèrent que l'efficacité, la tolérance et la présentation du méloxicam en suspension orale sont bien appropriées au traitement de l'ostéoarthrite chronique chez le chien.

(Traduit par docteur André Blouin)

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Introduction

Canine osteoarthritis (OA) is commonly encountered in veterinary practice. It is a syndrome characterized by deterioration of articular cartilage, bone remodeling and osteophyte formation, changes to the tissues surrounding the joint, and inflammation and pain. Curing canine OA, once it becomes clinically evident, is not currently possible. Current treatment strategies are directed towards slowing the progression of the disease and improving the general mobility, exercise tolerance, and quality of life of the dog. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of OA. The number of approved NSAIDs currently available for veterinary use is, however, limited. Furthermore, where treatment of OA is frequently life-long, very few NSAIDs are approved for long term use.

Meloxicam is an NSAID recently approved for use in dogs in Canada. Meloxicam is indicated for the treatment of inflammation and pain associated with acute and chronic musculoskeletal disease. The label dosage is 0.2 mg/kg body weight (BW) on day 1 followed by 0.1 mg/kg BW once daily (1).

Meloxicam is widely recognized as being one of the first commercially available cyclooxygenase type 2 (COX-2) selective NSAIDS (2–6). While COX-2 selective NSAIDs are believed to inhibit many of the inflammatory aspects of arachidonic acid metabolism, they are also believed to spare the "housekeeping" functions of prostaglandins and thromboxanes. The housekeeping duties of these arachidonic acid metabolites include the regulation of gastrointestinal blood flow and gastroprotective mechanisms, the regulation of renal blood flow, control of platelet aggregation and clot formation, and a host of other physiologic functions. The objective of the current study was to investigate the therapeutic efficacy and tolerance of meloxicam suspension in dogs suffering from chronic OA.

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Materials and methods

Animals

Forty dogs of mixed age, gender, breed, and body weight were enrolled in the trial. All animals were household pets and were initially selected from the case records of 7 veterinary practices in southwestern Ontario. All dogs included in the study had clinical signs of chronic OA (any or all of specific lameness, general stiffness, painful rise, or exercise intolerance). These clinical signs had been apparent within 2 wk preceding entry to the study. The dogs included in the trial had not been administered any medication other than heartworm and flea prophylaxis in the 2 wk preceding the study. Furthermore, the dogs had not received any long-acting corticosteroids within a 2-month period prior to study commencement. Informed consent was obtained from all owners prior to their dogs being entered in the study.

Dogs with clinical signs suggestive of the following conditions were excluded: spinal disk disease, gastrointestinal ulceration, impaired renal function, diabetes mellitus, osteoporosis, fracture, pregnancy, pyrexia, and myositis.

Study design

The study consisted of 2 phases. Phase 1 compared the therapeutic efficacy and tolerance of meloxicam or placebo under controlled conditions for 1 wk. Phase 2 involved further evaluation of the drug's clinical therapeutic efficacy and tolerance.

Phase 1 — Dogs were assigned to either drug or placebo treatment groups by using a computer-generated randomization table. Animals in the drug group were treated with meloxicam at a dosage of 0.2 mg/kg BW, PO, on day 1, followed by a reduction to 0.1 mg/kg BW, PO, q24h for a further 6 d. Animals in the placebo group were administered an equal volume of placebo by using the same dosing scheme. The study was blinded, so that neither the investigators nor the animal owners were aware of the dogs' treatment group. The drug (or placebo) was administered PO to all dogs on a small quantity of food.

Phase 2 — Following the initial 7 d of treatment, dogs assigned to the drug group continued to receive meloxicam at a dosage of 0.1 mg/kg BW, PO, q24h for a total of 28 d. Dogs assigned to the placebo group during Phase 1 were treated with meloxicam at a dosage of 0.2 mg/kg BW, PO, on day 1, followed by a reduction to 0.1 mg/kg BW, PO, q24h for a further 27 d.

Data parameters

Efficacy of the treatment was assessed by means of a clinical scoring system that assessed the animal's specific lameness, general stiffness, painful rise, exercise intolerance, and behavior (Table 1). Clinical scoring was performed by the investigating veterinarian prior to treatment, following 7 d of meloxicam or placebo administration, and following 4 wk of meloxicam administration.

The overall palatability of the drug, overall tolerance of drug treatment, and overall assessment of the dogs' quality of life were evaluated according to the parameters detailed in Table 2. Assessments were performed following 28 d of meloxicam therapy.

Table 1. Scoring system for assessment of clinical efficacy parameters

Clinical Parameter	Scoring System
Specific lameness	1 — No lameness
	2 — Mild (slight weight shift observed)
	3 — Moderate (marked weight shift observable, head shaking during walking)
	4 — Severe (severe lameness with intermittent toe touching or non-weight bearing)
General stiffness	1 — None (normal gait, stride length, no arching of back)
	2 — Mild (slight disturbance of gait, stride length, and/or slight arching of back)
	3 — Moderate (moderate disturbance of gait, stride length, and/or moderate arching of back)
	4 — Severe (severe disturbance of gait, extreme reduction in step length, and/or marked arching of back)
Painful rise	1 — Rises normally
	2 — Mild, rises slowly
	3 — Moderate, rises with difficulty
	4 — Severe, rises reluctantly or only with assistance
Exercise intolerance	1 — Normal
	2 — Mild, refuses to jump
	3 — Moderate, refuses to climb stairs
	4 — Severe, reluctance to walk
Behavior	1 — No abnormality (dog is willing and able to exercise without any signs of lameness or stiffness)
	2 — Minor abnormality (dog is willing and able to exercise but slight signs of lameness and/or stiffness are occasionally observed)
	3 — Moderate abnormality (dog is reluctant to exercise, obvious signs of lameness or stiffness observed)
	4 — Severe abnormality (dog is not able to do any exercise, permanent obvious signs of lameness and/or stiffness)

Blood from each animal was collected and analyzed for hematologic and serum chemistry parameters. These included red blood cell (RBC) count, differential white blood cell (WBC) count, total platelet count, packed cell volume (PCV), hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), serum urea, serum creatinine, total serum protein, serum albumin/globulin (A/G) ratio, and serum potassium. Analyses were performed for all animals preceding treatment, following 7 d of treatment with meloxicam or placebo, and following 28 d of treatment with meloxicam.

Test article

Dogs assigned to the drug group received an oral suspension of meloxicam (Metacam, 1.5 mg/mL meloxicam

Table 2. Scoring system for the assessment of the overall efficacy of meloxicam therapy and the overall palatability of meloxicam oral suspension

Clinical Parameter	Score	Scoring System
Overall quality of life	Excellent	The clinical signs observed at the first examination have disappeared. The physical condition is excellent.
	Good	Quality of life has improved. Obvious response to treatment.
	Moderate	Quality of life has slightly improved in comparison with the initial examination; minimal clinical improvement.
	Poor	The general clinical condition of the dog has remained unchanged or has worsened during the course of treatment.
Overall palatability	Good	The drug was accepted without problems.
	Satisfactory	The drug was accepted with some problems.
	Poor	The dog refused to take the product.

oral suspension, Boehringer Ingelheim Vetmedica, Burlington, Ontario). Dogs in the placebo group received the meloxicam oral suspension vehicle.

Statistical analysis

Data generated by the study were analyzed by Sapientia Scientific Services, Guelph, Ontario, using appropriate statistical tests. Associations were considered significant if $P < 0.05$.

Phase 1 — Clinical symptoms including specific lameness, general stiffness, painful rise, exercise intolerance, and quality of life, for the 2 treatment groups, placebo and drug, were tested by using an F-test with 1 degree of freedom for the treatment effect (equivalent to a *t*-test). This test was done for data on day 1 and on day 7.

Phase 2 — The clinical scores for the clinical signs mentioned above were subjected to a regression analysis where the independent variable was duration (day 0, day 7, and day 28). Regression coefficients were used to estimate scores for pre- and post-drug therapy.

Data for hematologic and serum chemistry parameters (dependent variables) were split into 2: ratio of responses below the normal reference range and ratio of responses above the normal reference range. These ratios were tested by using the linear logistic model and estimates of regression coefficients were obtained using the method of maximum likelihood (Logistic procedure, SAS/Stat 6th ed, SAS Institute, Cary, North Carolina, USA). The independent variable was time (day 0, day 28). The model was tested for goodness of fit and chi-squared analysis on the estimates was performed.

Results

The average age of the 40 dogs selected for entry to the trial was 9.2 y, $s = 3.3$. The most prevalent breeds were Labrador retriever (9/40), German shepherd (7/40), and golden retriever (6/40). The most common diagnosis was hip dysplasia (28/40); the remainder suffered from a range of arthritides involving the stifle, elbow, and/or shoulder joints.

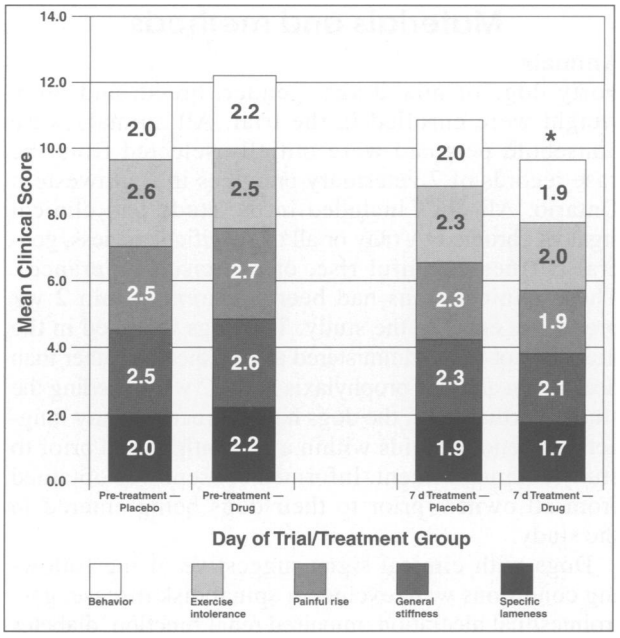

Figure 1. Clinical efficacy of meloxicam suspension for dogs in the drug and placebo groups following 7 d treatment. Numbers within bar refer to mean clinical scores for individual parameters. *Significantly different from pretreatment global score ($P < 0.05$), $n = 19$ for each group.

Of the original 40 clinical cases, 38 animals successfully completed the study. One animal died following 3 d of treatment with placebo. One dog's records and evaluation forms were retained by the animal's owner, who declined to pass them along to the investigators for inclusion in the trial.

Clinical assessments for specific lameness, general stiffness, painful rise, exercise intolerance, and behavior made following 7 d of meloxicam or placebo treatment were compared with initial pre-drug assessments (Figure 1). Significant reductions ($P < 0.05$) in the severity of clinical signs of disease were reported only for the drug group and not for the *placebo* group.

Evaluations performed following 28 d of meloxicam therapy, using an initial dose of 0.2 mg/kg BW followed by a maintenance dose of 0.1 mg/kg BW, q24h, demonstrated significant ($P < 0.05$) reductions in the severity of clinical signs of OA (Figure 2). Clinical scores for exercise intolerance were reduced by 26% and painful rise decreased by 29%; there was a 25% reduction in both general stiffness and specific lameness, while scores for behavior improved by 24%. It should be noted, however, that these measures were based on day 0 evaluations as a historical control group, and that a control cohort was not used in this phase of the study.

Data for the overall palatability of the drug, overall tolerance of drug treatment, and overall assessment of the drug's clinical efficacy are reported in Table 3.

There were no signs of intolerance to the drug or placebo in the first 7 d of the study. Data for the overall

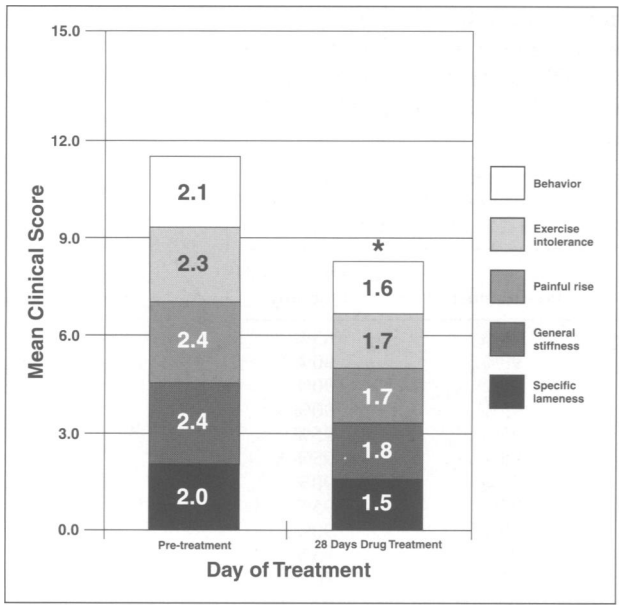

Figure 2. Clinical efficacy of meloxicam suspension for dogs administered 28 d therapy by using an initial loading dose of 0.2 mg/kg BW followed by a maintenance dose of 0.1 mg/kg BW q24h. Numbers within bar refer to mean clinical scores for individual parameters. *Significantly different from pre-treatment global score ($P < 0.05$), $n = 38$.

tolerance of meloxicam therapy revealed that on completion of 28 d of treatment, 4 of 38 dogs showed signs of possible mild intolerance to the drug, including isolated episodes of inappetence, diarrhea, vomiting, and fecal blood. One dog, however, had a history of occasional episodes of colitis/vomiting and another was prone to periodic diarrhea. It was not necessary to discontinue treatment or reduce the dosage of meloxicam administered in any of the dogs.

Hematologic values and serum chemistry measurements were presented as falling within, above, or below the normal reference range (Table 4). Pre-drug treatment data were tested against post-drug treatment data to determine if there was a change in parameters associated with prolonged meloxicam treatment. There were no definitive tendencies or trends in hematological or serum chemistry measurements. For all the parameters tested (RBC, WBC, total platelet count, PCV, hemoglobin, MCV, MCHC, serum urea, serum creatinine, total serum protein, serum albumin/globulin ratio, and serum potassium), there were no statistically significant changes above or below their respective normal reference ranges ($P > 0.05$).

Discussion

During the past decade, there has been an increased awareness of the medical importance of pain management in veterinary medicine (7,8). Nonsteroidal anti-inflammatory drugs are among the most widely used drugs in human medicine and have been used for decades for management of chronic pain. They have been widely and successfully employed in a variety of therapeutic applications in both man and animals; their primary use being in the treatment of inflammatory, degenerative,

Table 3. Overall clinical efficacy, palatability and tolerance of meloxicam treatment. Results are reported as percent of clinical cases

Clinical Parameter[a]	Score	Following 28 d Meloxicam therapy
Overall quality of life	Excellent	5%
	Good	82%
	Moderate	5%
	Poor	8%
Overall palatability of drug	Good	84%
	Satisfactory	13%
	Poor	3%
Overall tolerance of drug treatment	Excellent	89%
	Good	11%
	Moderate	0%
	Poor	0%

[a]$n = 38$ for each parameter

and painful conditions of the locomotor system. Nonsteroidal anti-inflammatory drugs are inhibitors of cyclooxygenase, the enzyme that ultimately converts arachidonic acid to prostanoids (thromboxane, prostacyclin, and prostaglandins), compounds that mediate inflammation (9).

Meloxicam is a selective COX-2 inhibitor derived from enolic acid (10). It has been documented to be effective in decreasing the local inflammatory response in a shoulder synovitis model in dogs (11) and in attenuating stifle synovitis and associated lameness induced by sodium urate in this species (12). This investigation demonstrates the effectiveness of meloxicam in treating chronic locomotive disorders in the dog. Meloxicam significantly reduced specific lameness, general stiffness, painful rise, and exercise intolerance of the dogs participating in the study, while greatly improving their quality of life. It should be noted, however, that a negative control group was used for only the first 7 d, after which humane concerns made this option untenable. At the owner's insistence, 17 dogs were maintained on meloxicam treatment following the conclusion of the study. At the time of writing, efficacy has been maintained for at least 22 mo with no adverse effects noted.

Dogs are quite susceptible to the adverse effects of NSAIDs and safety data from other species, especially humans, cannot be extrapolated to the dog (8). The use of NSAIDs approved only for human use can carry appreciable risk when these drugs are administered to dogs (13). These drugs are recognized to induce specific side effects in animals and humans by virtue of their mode of action. Inhibition of the production of endogenous gastric prostaglandin E_2 (PGE_2) can affect gastric mucus production, mucosal blood flow, and acid secretion, which may give rise to gastrointestinal irritation and ulceration (14). Inhibition of vasodilatory PGE_2 and PGI_2 production in the kidney, particularly in hypovolemia, can lead to compromised renal perfusion (15). A host of other possible side effects have been reported but are much less common than are gastrointestinal and renal effects.

Meloxicam was well tolerated by the dogs in this trial. Of the 4 dogs that experienced adverse effects, all

Table 4. Hematologic and serum chemistry data for animals (n = 38) treated with meloxicam using an initial dose of 0.2 mg/kg BW followed by a maintenance dose of 0.1 mg/kg BW q24h for 28 d in total. Results are reported as percent of clinical cases falling within the normal reference range per assessment point

Hematology or serum chemistry parameter	Normal reference range	% of cases within normal reference range Time of Assessment	
		Pre-treatment	Following 28 d of therapy
RBC count	5.5–8.2 × 10^{12}/L	100%	85%
WBC count	6.6–18.4 × 10^{9}/L	90%	80%
Total platelet count	150–450 × 10^{12}/L	90%	90%
PCV	0.37–0.55 L/L	95%	90%
Hemoglobin	126–194 g/L	95%	95%
MCV	65–75 fl	95%	95%
MCHC	320–360 g/L	75%	90%
Urea	2.1–8.9 mmol/L	95%	95%
Creatinine	53–145 mol/L	90%	90%
Total protein	54–76 g/L	95%	95%
A/G ratio	0.6–1.3	85%	80%

RBC — red blood cell; WBC — white blood cell; PCV — packed cell volume; MCV — mean corpuscular volume; MCHC — mean corpuscular hemoglobin concentration; A/G — albumin/globulin

experienced transient clinical signs that did not require alteration of the dose of meloxicam or other therapeutic intervention. Furthermore, 2 of these dogs had a history of gastrointestinal disease prior to the start of the study. Our findings in this regard are consistent with published data that has demonstrated the considerable gastrointestinal tolerance to meloxicam (16–19). Renal function, as assessed by measurements of serum urea and creatinine, did not appear to be affected. It should be noted, however, that elevations in these biochemical parameters would only be noted in advanced renal compromise. Our findings are consistent with published data supporting the renal safety of meloxicam (20).

Meloxicam oral suspension proved very palatable and was accepted without problems in the majority of cases. Furthermore, the liquid formulation allowed owners to administer the required dosage easily and accurately.

The findings of this investigation suggest that the efficacy, tolerance, and formulation of meloxicam oral suspension make it well suited for the treatment of canine chronic osteoarthritis. CVJ

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