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Amantadine in a Multimodal Analgesic Regimen for Alleviation of Refractory Osteoarthritis Pain in Dogs

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) do not always provide sufficient pain relief in dogs with osteoarthritis (OA).

Hypothesis: The use of amantadine in addition to NSAID therapy will provide improved pain relief when compared with the use of nonsteroidal analgesics alone in naturally occurring OA in dogs.

Animals: Thirty-one client-owned dogs with pelvic limb lameness despite the administration of an NSAID.

Methods: The study was randomized, blinded, and placebo controlled with parallel groups (days 21–42). On day 0, analgesic medications were discontinued. On day 7, all dogs received meloxicam for 5 weeks. On day 21, all dogs received amantadine (3–5 mg/kg once daily per os) or placebo for 21 days, in addition to receiving meloxicam. Assessments were performed before the study and on days 7, 21, and 42. Primary outcome measures were blinded owner assessments of activity using client-specific outcome measures (CSOM) on days 0, 7, 21, and 42. Data were analyzed by a mixed model approach.

Results: For CSOM activity, there was a significant time by treatment effect ($P = .009$). On the basis of the planned post hoc *t*-tests of postrandomization means, there was a significant difference between treatment groups on day 42 ($P = .030$), with the amantadine group being more active.

Conclusions and Clinical Importance: In dogs with osteoarthritic pain refractory to an NSAID, physical activity is improved by the addition of amantadine. Amantadine might be a useful adjunct therapy for the clinical management of canine osteoarthritic pain.

Key words: Dog; Nonsteroidal anti-inflammatory; Owner; Pain; Subjective assessment.

Osteoarthritis (OA) is a prevalent disease in both humans and dogs. The presence of pain, assumed because of the improved function when nonsteroidal anti-inflammatory drugs (NSAIDs) are administered, in naturally occurring OA in dogs has been well established.[1–4] The pain associated with the disease causes decreased physical activity. In the absence of a cure for the disease, and when joint replacement is not feasible, the primary goal in most human patients is to alleviate the pain through pharmacological methods.[5–7] NSAIDs are not always completely effective against the pain of OA in humans.[8–10] Clinical experience[11] and a review of experimental studies[1,3,4] clearly reveal that NSAIDs do not provide complete pain relief in dogs with OA. As a result, adjunctive analgesics are used in combination with NSAIDs in human patients,[12–15] and a similar approach has been suggested in dogs.[11] However, to date, no studies have evaluated the efficacy of any multimodal drug approach in dogs with OA.

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The pain associated with OA is considered to be chronic pain and in humans has been shown to be associated with sensory disturbances similar to those found in so-called neuropathic pain.[16,17] Experimentally, it has been established that the *N*-methyl D-aspartate (NMDA) receptor is involved in the neurobiological changes underlying these sensory disturbances in prolonged inflammatory and neuropathic pain.[18,19]

Amantadine was first recognized as an antiviral agent[20] and was later found to be useful in treating Parkinson's disease.[21,22] Although initially thought to be caused by effects on the dopaminergic system, its effectiveness in treating nervous system disorders appears to result predominantly from its inhibition of NMDA responses.[23] Amantadine seemingly encourages NMDA receptors to occupy closed conformations, and its interactions with the NMDA receptor make it particularly effective at inhibiting NMDA responses during prolonged depolarizations that accompany neurological insults, such as might occur in chronic pain.[24] Amantadine administered IV abolished or reduced pathological pain in humans with chronic neuropathic pain[25] and in cancer patients with surgical neuropathic pain.[26] However, amantadine PO appeared not to be analgesic in 10 humans with various types of neuropathic pain.[27] More recently, amantadine PO reduced experimental sensitization and pain in humans with chronic back pain.[28] The analgesic effects of amantadine in dogs with chronic OA pain have not been investigated, to our knowledge.

Using dogs with naturally occurring OA pain that was refractory to NSAID treatment, we hypothesized that the use of amantadine in addition to NSAID therapy would provide improved pain relief when compared with the use of nonsteroidal analgesics alone.

Materials and Methods

This study was approved by the Animal Care and Use Committee at North Carolina State University and the Animal Anesthesia & Pain Management Center and was in accordance with the National Institutes of Health and the International Association for the Study of Pain policies on the use of clinical subjects. The study was a randomized, blinded, placebo-controlled design using a naturally occurring OA in dogs.

Animals

Thirty-one client-owned dogs with clinical pelvic limb OA-related lameness despite the use of an NSAID were recruited to the study. One site (NCSU) recruited 20 dogs, whereas the other site (Animal Anesthesia and Pain Management Center, Colorado Springs) recruited 11 dogs. All owners gave written informed consent.

Inclusion Criteria

To be included in the study, it was decided a priori that eligible dogs were required to (a) have lameness and owner-identified mobility impairment despite the use of an NSAID, (b) exhibit a painful response upon manipulation of at least 1 pelvic limb appendicular joint that also had radiographic changes consistent with OA, (c) be free from clinically significant abnormal hematological or blood chemistry values, and (d) be free from clinically detectable systemic disease. The lameness and activity impairment had to have been present for at least 3 months despite the use of an NSAID at an approved or what would be considered a "full" dose (doses of nonapproved NSAIDs recommended in veterinary drug formularies) over that period of time. OA was confirmed radiographically and lameness and joint pain were confirmed on physical examination within 7 days of initiation of the study. Administration of glucosamine-chondroitin sulfate preparations was acceptable as long as the administration of these had been ongoing for at least 10 weeks, and their administration was not changed during the study period. Dogs were excluded from the study if impending changes such as moving residence, marriage, vacations, or introduction of new pets or people into the household were expected during the study period. Dogs were excluded if they had received a long-acting analgesic/anti-inflammatory preparation within 8 weeks of the study.

Experimental Protocol

After screening of potential candidates, a total of 31 dogs were recruited to the study. Medications were discontinued on day 0. On day 7, all dogs received meloxicam (0.1 mg/kg once daily per os after a 0.2 mg/kg initial dose on the first day of medication [FDA approved dosing]) for 5 weeks. On day 21, the randomized, placebo-controlled, blinded portion of the study began. Dogs were randomly allocated to receive amantadine (group A) (3–5 mg/kg once daily per os) or placebo (group P) for 21 days, in addition to meloxicam. The amantadine dose was decided on the basis of its kinetics,[29] clinical observations, and pilot data. Randomization was ensured by computer-generated lists generated for each center by the NCSU pharmacy. The identical-looking placebo was compounded by the NCSU pharmacy. Dogs were dosed with whole capsules. Dogs weighing 20–37.5 kg were administered 1 capsule (100 mg) once daily, and dogs weighing 37.5–67 kg were administered 2 capsules daily (200 mg). The placebo dosing was identical. A pharmacist at each test site was responsible for the prescription of drugs and placebo. Other investigators were blinded to the treatments. Assessments were performed on days 0 (before the study), 7, 21, and 42. The primary outcome measures were blinded owner assessments by means of client-specific outcome measures (CSOMs).[30,31] Secondary outcome measures were (1) a standard orthopedic questionnaire; (2) a blinded assessment of lameness, weight bearing, and reaction to joint manipulation made by a veterinarian; and (3) clinico-pathological data (CBC, chemistry, UA) (days 0, 21, and 42).

CSOM Activity

Before the study, owners were questioned and the specific activities that were problematic for their dog were defined in detail. Examples of activities were given to the owner to prompt discussion. After discussion, owners were directed to describe 5 time- and place-specific activities that they considered were altered, and to grade the degree of impairment compared with a precise age when they considered their dog's activity was normal. These were used to complete the "CSOM" form (Appendix 1 [30,31]). For example, instead of describing stair climbing ability as "stair climbing," the time and place that this was noticed was included: "ability to climb up the steps at the back of the deck in the evening." A single investigator (BDXL or JG) directed each CSOM construction at each center. This resulted in a unique set of activities for each dog. After completion of the CSOM form on day 0, the same unique set of activities was assessed at each visit to the clinic on days 7, 21, and 42 by a single technician at each site. Owners were not permitted to see how they had previously graded activity impairments. The CSOM was also completed by telephone on days 14, 28, and 35. This was performed to ensure that owners remained focused on the activities they were evaluating.

CSOM Behavior

In a manner similar to the activity assessments, the altered behavior was assessed (Appendix 1). In that assessment, the behavior was graded as occurring either significantly less than normal, less than normal, a normal amount, more than normal, or significantly more than normal. Again, this assessment was made in comparison to a chosen age when the owners considered their dog to be normal. Behavior CSOMs were assessed at the same time as activity CSOMs.

Standard Orthopedic Questionnaire

A standard orthopedic questionnaire (Appendix 2) was completed by owners at the same time as the CSOMs.

Veterinarian Assessment of Lameness, Weight Bearing, and Response to Palpation

These parameters were assessed by means of a subjective evaluation system (after Budsberg et al[3]) shown in Appendix 3. Evaluations were performed by the investigators (BDXL, JG, DM-L, and SR) or surgery residents. No attempt was made to have the same investigator perform all assessments in any given dog. Both pelvic limbs were evaluated, but data were analyzed only for the most affected limb, which was defined at the start of the study. The joint that was manipulated was defined at the start of the study.

Data Analysis

Because of the distributions of the variables and the small sample size, the age and weight distribution of the dogs in each group was compared by means of the Wilcoxon rank sums test. The limb most affected (right or left pelvic limb) was compared between the groups by means of Fisher's exact test.

The ratings of impaired mobility, behavior changes, standard orthopedic assessment, and veterinarian assessment of lameness, weight bearing, and response to palpation were converted to an ordinal scale (Appendix 1–3). These values were summed for each

dog at each visit. For example, this resulted in a possible range of 0 (no problems) to 20 (all listed activities impossible) for activity, and 0 (normal behavior) to 6 (all behaviors significantly altered [increased or decreased]) for behavior.

The focus of statistical analysis was to determine whether there were differences between the groups over the time period from days 21 to 42. A mixed linear model was used to determine whether there were differences between treatment groups over time from days 21 to 42. The model assumes a linear change in means between treatments over time and a compound-symmetry covariance structure (constant variance and constant covariance). Because randomization to placebo or amantadine occurred on day 21, the day 21, 28, 35, and 42 measurements were included in the model. If a significant time by treatment effect was found, post hoc *t*-tests for differences between treatments at the day 42 time point were performed.

To examine for differences within groups over time for the CSOM data, we again fit mixed linear models within each group, looking for an overall difference in means over time. All time points were included in the models. If the overall effect for time period was significant, we performed *t*-tests to test for specific preplanned differences between time points (days 0 and 7, days 7 and 21, and days 21 and 42). Because of the relatively small number of comparisons being performed, a Bonferroni adjustment was not applied, as this was considered too conservative.

Urine and blood parameters were also evaluated by means of the Wilcoxon rank sums test to test for differences between groups. All analyses were conducted at $\alpha = 0.05$.

Table 1. Client-specific outcome measures–activity scores at assessment time points for the placebo (P) and amantadine (A) groups, and indication of *P*-values for statistical comparison between groups during the placebo-controlled, blinded portion of the study (days 21–42).

Variable	Treatment	Mean	SD	*P*-Value
Day 0	P	11.4	1.98	
	A	9.6	2.67	
Day 0 difference		1.8		
Day 7	P	10.6	3.27	
	A	9.8	2.96	
Day 7 difference		0.8		
Day 14	P	8.6	3.54	
	A	7.8	3.89	
Day 14 difference		0.8		
Day 21	P	6.9	3.12	
	A	7.1	3.50	
Day 21 difference		0.2		
Day 28	P	5.5	3.37	
	A	5.4	3.43	
Day 28 difference		0.1		.909
Day 35	P	4.7	3.38	
	A	5.5	4.51	
Day 35 difference		− 0.8		.558
Day 42	P	6.7	3.91	
	A	3.9	2.87	
Day 42 difference		2.8		.030

Results

There were no significant differences detected in the age, weight, or duration of previous treatment between groups A and P. The median (range) age of the dogs in groups P and A was 9.0 (1–13) and 9.5 (4–15) years, respectively. The median (range) weight of the dogs in groups P and A was 31.0 (20.5–43) and 32.4 (23.8–53.4) kg, respectively. The median (range) duration of previous treatment with NSAIDs in groups P and A was 2.0 (0.5–4) and 2.0 (0.5–3) years, respectively. The NSAIDs used before the study started were aspirin, carprofen, deracoxib, etodolac, firocoxib, and meloxicam. Only 2 dogs had received meloxicam.

Forty-one percent (7/17) of the dogs receiving amantadine had the right pelvic limb as the limb most affected compared with 57% (8/14) in those receiving placebo. This difference was not statistically significant ($P = .480$).

Group P had an activity impairment that was higher than group A on day 0 ($P = .047$). By day 7, the scores did not differ ($P = .367$). For CSOM activity scores, there was a significant overall effect of time period in the models for both treatment groups ($P < .0001$). There was no significant change from days 0 to 7 in either group. From days 7 to 21, there were highly significant differences (improvements in activity) within each group (nonblinded portion of study). By day 21, both groups had nearly identical CSOM scores. From days 21 to 42 there was a significant improvement in the amantadine group ($P = .0003$) but not the placebo group.

For CSOM activity over days 21–42, the model indicated a significant time by treatment effect ($P = .009$). On the basis of the planned post hoc *t*-tests of postrandomization means, there was a significant difference between treatment groups on day 42 ($P = .030$) (Table 1), with the amantadine group assessed as being significantly more active.

For CSOM behavior scores, there was a significant overall effect of time period in the models for both treatment groups ($P < .0001$ for the amantadine group and $P = .048$ for the placebo group). The change between days 7 and 21 was statistically significant in the amantadine group ($P = .014$). There were no significant differences in CSOM for behavior between groups at any time point in the day 21–42 period ($P = .25$).

There were no significant differences in the distribution of summary scores from the standard orthopedic questionnaire between groups at any time point in the day 21–42 period ($P = .768$).

For the orthopedic lameness results, the model indicated a significant time by treatment effect ($P = .029$). On the basis of the planned post hoc *t*-test of postrandomization means, there was a significant difference between treatment groups on day 42 ($P = .03$), with group A being assessed as less lame on the veterinarian assessment (Table 2).

There were no significant differences in the distribution of the weight-bearing evaluations between groups at any time point in the day 21–42 period ($P = .66$).

For the joint flexion results, the model indicated no time by treatment effect ($P = .784$).

There was a statistically significant difference in alkaline phosphatase (ALP) from days 21 to 42 between the groups ($P = .049$). ALP dropped by a mean of 8.3 U/L in group P and rose by a mean of 2.3 U/L in group A.

In 5 dogs (3 from group A, 2 from group P), ALP was outside the reference range at the start of the study

Table 2. Veterinarian orthopedic evaluation scores (lameness) at assessment time points for the placebo (P) and amantadine (A) groups, and indication of differences between the groups at time points with the *P*-value for statistical comparison at day 42.

Variable	Treatment	Mean	SD	*P*-Value
Day 0	P	1.6	0.63	
	A	1.8	0.53	
Day 0 difference		−0.2		
Day 7	P	1.6	0.84	
	A	1.5	0.87	
Day 7 difference		0.1		
Day 21	P	1.3	0.61	
	A	1.2	0.83	
Day 21 difference		0.1		
Day 42	P	1.4	0.85	
	A	0.8	0.83	
Day 42 difference		0.6		.028

(levels of 150–256 U/L), and remained approximately stationary. Alanine aminotransferase (ALT) was outside the normal range in 4 dogs at the start of the study (levels of 133–277 U/L). In 2 dogs (group A) it dropped into the normal range; in 1 (group A) it stayed the same, and in 1 it rose from 277 to 390 U/L (group P). In 3 dogs (2 from group A, 1 from group P) blood urea nitrogen (BUN) was slightly raised at the start of the study and remained slightly raised. In 2 dogs (group A), BUN was slightly raised at day 21 (29 and 32 mg/dL; normal range 8–27 mg/dL), and dropped in 1 and remained at that level for the other by day 42.

Discussion

In this study, using dogs with OA pain that was refractory to NSAID treatment, the ability to perform everyday activities in subjects with mobility impairment was improved by the addition of amantadine to the NSAID therapy. The dogs in this study had OA of the stifle as a result of cranial cruciate pathology[32] or of the hip as a result of hip dysplasia,[33–35] and the disease was considered secondary OA.

NSAIDs are not always completely effective against the pain of OA in humans.[8,9] Clinical experience[11] and a review of experimental studies[1,3,4] clearly reveal that NSAIDs do not provide complete pain relief in dogs with OA.[1,3,4] This is probably because of the incomplete suppression of the intermittent peripheral inflammatory processes, and also the fact that NSAIDs act on only certain aspects of the complicated nociceptive processing. The extensive central changes accompanying chronic pain mean there is a requirement for a multimodal approach in order to effectively manage pain.[5,36–38] Despite this knowledge, the use of a multimodal drug treatment approach for OA pain in dogs has received virtually no attention in the veterinary literature.

Changing NSAID is 1 strategy that the authors (BDXL and JG) have used in trying to more effectively manage refractory OA pain. The results of this study suggest that this strategy can be effective, although this part of the study was not placebo controlled. Neither group significantly deteriorated when the original NSAID therapy was stopped, and both groups improved over a 14-day period when meloxicam was introduced. Only two of the dogs had previously been medicated with the NSAID meloxicam.

Despite the improvement seen with switching from the original NSAID to meloxicam, all the dogs were still impaired and considered to be in pain. Chronic pain is associated with multiple changes in the neurobiology of the central nervous system. The central nervous system is plastic,[39] and noxious inputs from the periphery can produce central sensitization. The principal receptor involved in this plasticity is the NMDA receptor.[40] NMDA-mediated "cellular windup" results in central sensitization. Central sensitization contributes to injury or disease-induced pain by causing amplification of the signals and encoding previously nonnoxious signals as noxious.[41,42] Although the role of the NMDA receptor in naturally occurring OA has not been investigated, it has been shown to play a role in noxious stimulus processing in rodent models of arthritis.[43,44] Amantadine, an NMDA receptor antagonist, might be beneficial in chronic pain states by decreasing central sensitization. Amantadine has been used for the treatment of neuropathic pain in humans[25,26] but, as yet, has not been evaluated in any species for the alleviation of pain associated with OA. It would be expected that amantadine would be more likely to be effective in patients with central sensitization. There is no validated assessment of sensory dysfunction in dogs such as the quantitative sensory tests (QSTs) that have been used in trials of amantadine in humans.[28] However, thermal and mechanical threshold testing has been successfully used in other situations in cats[45–47] and in dogs,[48–50] and such techniques could potentially be applied to dogs with naturally occurring OA to determine whether central sensitization is present.

The primary outcome measure used in this study was the CSOM. Recently, our laboratory evaluated this owner-based subjective system against a validated objective measure of distance moved in cats with naturally occurring OA.[51,52] These studies highlighted the need for a placebo group, but indicated that owners are able to assess when their pet is able to move more in response to analgesic therapy. Recent studies in dogs have indicated that owners can be used to assess pain in their pet dogs,[53] and that veterinarian assessments are not as sensitive as owner assessments, with owner assessments in fact agreeing with force plate evaluations, and veterinarian assessments not.[a] In the present study, 50% of the activities chosen by owners for assessment were getting up from lying down, getting into the car, climbing stairs, walking on slick floors, moving after rest after a walk, and getting onto furniture. Our secondary outcome measures of the general orthopedic questionnaire and the majority of the veterinarian assessments (except the lameness evaluation) did not indicate any differences between the groups. It is likely that the general orthopedic questionnaire was not sensitive enough in contrast to the CSOM that picked out individual activities that were

impaired. The approach of using activities that are specific to the individual patient is similar to goal attainment scaling in human medicine.[54,55]

There were no significant changes in the CSOM for behavior. This may be because this was an inappropriate measure. Validation of CSOM-behavior scales has not been performed, and although it has been shown that dogs with pelvic limb OA result in altered activities,[53,56] only very recently have other behavioral effects of OA been investigated.[57] The most frequent behaviors considered abnormal by owners in this study were restlessness, sociability, aggression, anxiety, vocalization for attention, and dependence on the owner. It may well be that behaviors that may have a significant learned component do not change as quickly as activity, or, indeed, that behaviors were favorably altered, but amantadine produced adverse behavioral changes of its own.

No significant effects of amantadine administration on CBC, blood chemistry, or urine analysis were seen in this study, and no adverse effects were noted by owners. These findings are similar to the published toxicological studies on amantadine in dogs, where no effects on blood variables were seen after administration of amantadine for up to 2 years, at doses of 8, 40, or up to 80 mg/kg, despite deaths occurring at the higher doses because of seizure activity.[58] Amantadine is excreted by the kidney in dogs,[29] and caution is recommended when using amantadine in human patients with decreased renal function.[59,60]

In dogs with NSAID-refractory osteoarthritic pain, function is improved by the addition of amantadine. The improved function appears to be because of pain relief. Amantadine may be a useful adjunct therapy for the clinical management of dogs with osteoarthritic pain.

Footnote

[a] 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. Proceedings of the 36th Annual ACVS Scientific Meeting (Small Animal), 2001:11

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Appendix 1

Client-Specific Outcome Measures – Activity

Problems in mobility related to osteoarthritis (numbered 1–5)	Indicate how problematic these activities are compared with when your dog was normal or did not have osteoarthritis. Comparison is to when he/she was _ years old.				
	No problem	A little problematic	Quite problematic	Severely problematic	Impossible
Score assigned for statistical analysis →	0	1	2	3	4
1					
2					
3					
4					
5					

Client-Specific Outcome Measures – Behavior

	Indicate the frequency of these behaviors compared with when your dog was normal or did not have osteoarthritis. Comparison is to when he/she was _ years old.				
Changed behavior as a result of the osteoarthritis	Significantly less than normal	Less than normal	Normal amount	More than normal	Significantly more than normal
Score assigned for statistical analysis →	2	1	0	1	2
1					
2					
3					

Appendix 2

Standard Orthopedic Questionaire

How difficult are these activities for your dog?	No problem	A little problematic	Quite problematic	Severely problematic	Impossible
Score assigned for statistical analysis	0	1	2	3	4
Walking					
Running					
Jumping					
Getting up					
Lying down					
Climbing stairs					
Descending stairs					

Appendix 3

Left	Score assigned for statistical analysis	Right
		Lameness
	0	Trots normally
	1	Slight lameness at a trot
	2	Moderate lameness at a trot
	3	Severe lameness at a trot
	4	Severe lameness at a trot
		Weight bearing
	0	Normal weight bearing at rest and a trot
	1	Partial weight bearing at rest and normal at a trot
	2	Partial weight bearing at rest and at a trot
	3	Partial weight bearing at rest and nonweight bearing at a trot
	4	Nonweight bearing at rest and at a trot
		Response to affected joint flexion and extension
	0	No response
	1	Mild response (turns head toward affected joint)
	2	Moderate response (withdraws affected joint)
	3	Severe response (vocalizes or becomes aggressive)
	4	Disallows manipulation or palpation of affected joint