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Dose Reduction of Meloxicam in Dogs with Osteoarthritis-Associated Pain and Impaired Mobility

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Background: Progressive nonsteroidal anti-inflammatory drug (NSAID) dose reduction appears logical; however, there is no evidence-based medicine indicating that efficacy is maintained as dose is reduced.

Objective: To determine if NSAID dose can be reduced and pain relief and mobility can be maintained in dogs with osteoarthritis (OA).

Animals: Client-owned dogs (n = 59) with OA-associated impaired mobility and pain.

Methods: Prospective, randomized, blinded study. After 14 days wash-out, dogs were randomized to reducing dose (RDG) (n = 30) or maintenance dose (MDG) (n = 29). MDG received standard dose meloxicam. RDG received a reducing dose from D28 onward, reducing to 0% of maintenance for the final 2 weeks. Assessments were at D14, 28, 42, 56, 70, 84, 98 and 112 using subjective owner assessments, accelerometry (AM), and standing percent body weight distribution (%BW). A Kaplan–Meier survival curve described how dogs dropped out because of insufficient pain control. A Log-rank test compared the groups.

Results: More dogs in RDG (13) dropped out because of owner-evaluated insufficient pain control compared with MDG (5) ($P = .029$; odds ratio: 3.67; median dropout time: 84 days in each group). For the dogs that did not drop out (n = 41), there were no significant differences between groups in owner assessments ($P > .2$ for each), %BW placed on the index limb ($P = .750$), or accelerometer-measured activity ($P = .14$).

Conclusion and Clinical Relevance: Dose reduction is a less effective means of pain control compared with maintained dosing. However, NSAID dose reduction with maintained efficacy is possible, but success appears to be individual dog dependent.

Key words: Arthritis; Chronic; Nonsteroidal anti-inflammatory drug.

Osteoarthritis (OA) is a common condition affecting over 20% of dogs over 1 year of age.[1] Pain and disability are the clinical signs associated with OA, and the current therapeutic practice is the promotion of long-term continuous use of nonsteroidal anti-inflammatory drugs (NSAIDs) as part of a multimodal approach to the management of the dogs with OA.[2] However, despite proven efficacy, the adverse effects of NSAID administration for dogs with OA have been well documented.[2–5] Despite no evidence to support an increased risk of adverse effects with increasing duration of NSAID administration,[2] it is the recognition of these adverse effects that has led to dose reduction over time being a suggested clinical approach.[4] Clinically, dose reduction is achieved either by gradually reducing the total daily dose administered or reducing the frequency of administration. However, despite dose reduction appearing to be a logical step to employ in the medical management of OA-associated pain, to date, there has been no evidence-based medicine to prove that efficacy is maintained as the dose of NSAID is reduced.

Abbreviations:

AM	activity monitor
CBPI	canine brief pain inventory
CBPIi	canine brief pain inventory score for interference factors
CBPIp	canine brief pain inventory score for pain
CBPIt	total canine brief pain inventory score
CSOM	client specific outcome measures
DJD	degenerative joint disease
HCPI	Helsinki Chronic Pain Index
MDG	maintained dose group
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
PVF	peak vertical force
RDG	reduced dose group

Meloxicam is an NSAID approved for use in dogs for the treatment of inflammation and pain associated with acute and chronic musculoskeletal disease. The clinical efficacy and appropriate safety of long-term meloxicam use in the management of dogs with OA have been well documented,[2,6–9] and its oral suspension formulation makes it an ideal product for use in dose-reduction studies. We hypothesized that pain relief and activity are maintained in dogs with painful OA receiving a gradually reducing dose of meloxicam. The primary objectives were to (1) determine whether the dose of meloxicam administered to dogs with OA-associated pain can be reduced while maintaining pain relief and mobility; and (2) determine the degree of dose reduction that can be achieved (expressed as a

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percentage of the original maintenance dose) while maintaining efficacy.

Materials and Methods

The clinical study protocol was approved by the Institutional Animal Care and Use Committee at North Carolina State University (#08-077-O). Owners gave informed consent. The study was a blinded, parallel group, placebo-controlled clinical study with an intent to treat analysis.

Animals

The aim was to recruit 60 client-owned dogs with OA-associated pain and impaired mobility. Dogs of any breed, age, sex, or weight were recruited by e-mail and local newspaper advertising, and by direct telephone contact in the case of previous clients. Group size was based on power calculations using data available to the authors using the Helsinki Chronic Pain Index (HCPI), which was subsequently published.[10] Assuming that a decrease in NSAID efficacy of 50% would be unacceptable, we calculated that 31 dogs would be needed in each treatment group for a study power of 0.8 (at a two-sided 5% significance).

Evaluation of Potential Study Candidates (Screening)

To be eligible for screening, dogs were required to have impaired mobility (according to their owners), have not received oral or parenteral steroids or injectable polysulphated glycosaminoglycans within the last 4 weeks. and owners were required to agree to stop administering NSAIDs before the start of the study. The screening evaluation included a physical, neurologic, and orthopedic examination, and a complete blood count (CBC), serum biochemical analysis and urinalysis. Exclusion criteria included the presence of suspected or demonstrated systemic or local disease other than OA. Dogs were also excluded if they were suffering from recent joint instability, such as cranial cruciate ligament rupture or had undergone joint surgery within the previous 12 months.

Results of all laboratory testing must have been either within the reference range values or considered clinically nonsignificant. If alanine aminotransferase or alkaline phosphatase were $\geq$ twice the high end of the reference range, then pre- and postprandial bile acid tests were performed. If the postprandial bile acid value was within the reference, the dog was considered an acceptable candidate for the study.

Digital radiographs of all clinically abnormal (painful) appendicular joints were taken under sedation using an indirect digital flat panel imaging system.[a] Dogs with no detectable systemic disease, and with at least 1 appendicular joint where manipulation elicited an aversive response and whose radiographs showed the presence of OA, were included. Dogs were designated as being either predominantly "forelimb" or "hind limb" impaired, and the limb most adversely affected by OA pain was designated the index limb.

Owners were required to have a stable routine of daily living that was unlikely to change over the 16 weeks of the study.

Group Assignment

Enrolled dogs were categorized as having either "high" or "low" degrees of impaired mobility. Low impairment was a CBPI score of 1–50 on Day 0; high impairment was a CBPI score of 51–100. Dogs were further subclassified as either having predominantly forelimb or hind limb pain, and each dog was assigned one of the following 4 groups: high impairment/fore limb, high impairment/hind limb, low impairment/fore limb, and low impairment/hind limb.

Study Protocol

The study was a blinded, parallel group, placebo-controlled, clinical study over a 16-week period. On Day 14, dogs were randomly assigned, by way of a 4-block design stratified for the 4 permutations listed above, to either a reducing dose group (RDG) or maintenance dose group (MDG). During the study, groups were only known as A or B.

In the MDG, dogs were administered meloxicam[b] at an initial loading dose of 0.2 mg/kg PO, once in the evening, with food, on Day 14, followed by 0.1 mg/kg PO, every evening, with food, for the duration of the 16-week study. In the RDG, dogs were administered meloxicam at an initial loading dose of 0.2 mg/kg PO, once in the evening, with food, on Day 14, followed by 0.1 mg/kg PO, every evening, with food, for 2 weeks. From Day 28, the concentration of meloxicam was diluted with a placebo (visually identical to regular meloxicam solution; prepared by the NCSU pharmacy[c]) so that the concentration was reduced as outlined in Table 1. The volume of drug or drug/placebo mix administered (on all study days except the first day of dosing) was kept at 0.67 mL/kg throughout the study in both groups. Meloxicam/placebo was dispensed in identical NCSU pharmacy-labeled bottles every 14 days, and previous bottles were collected.

Recheck evaluations were performed on Days 14, 28, 42, 56, 70, 84, 98, and 112. The first 5 dogs in the study finished at D84, as this was the original end date of the study. After the completion of the first 5 dogs without any apparent deterioration, the study was extended to 112 days, with further dose reduction, for all remaining and subsequent dogs.

Dogs were only withdrawn from the study prematurely for 3 reasons: (1) the dog was not tolerating the medication; (2) the dog developed a condition that would have excluded it from commencing the study such as acute cranial cruciate ligament rupture; (3) the owner reported that they felt that their pet's pain control was no longer acceptable. It was not part of the remit of this study to see if pain control increased again with increasing doses of meloxicam.

Outcome Measures

Primary outcome measures were the number of dogs in each group that dropped out of the study because of pain control being insufficient (as determined by the owner); the HCPI; the

Table 1. Outline of the percentage of the recommended maintenance dose of meloxicam (% of 0.1 mg/kg/day) that dogs in each group were administered. Volumes of medication were maintained at 0.67 mL/kg.

	Maintained Dose Group	Reduced Dose Group
Days 0–13	0	0
Days 14–27	100	100
Days 28–41	100	85
Days 42–55	100	70
Days 56–69	100	55
Days 70–83	100	40
Days 84–97	100	20
Days 98–112	100	0

canine brief pain inventory (CBPI); activity monitor (accelerometer) counts (AM); and percent body weight distribution measurements ($\%BW_{distrib}$).

Secondary outcome measures were client-specific outcome measures (CSOM) and client records of adverse events.

Owner Assessed Pain Control

At the end of each visit, owners were asked whether they were "happy with their dog's current pain control." If they were, the dog continued in the study. If they were not, the dog dropped out of the study.

Helsinki Chronic Pain Index

The HCPI is an 11-item questionnaire that has been described elsewhere.[10,11] Owners answered 11 questions based on a 5-point descriptive scale and the score calculated.

Canine Brief Pain Inventory

The CBPI (a 2-factor, 11-item questionnaire)[12,13] contains 4 questions pertaining to the severity of pain evident in a dog (pain severity score, CBPIp), 6 questions pertaining to how the pain interferes with the dog's typical activities (pain interference score, CBPIi), and 1 question on global quality of life. Total CBPI (CBPIt), pain severity, and pain interference scores were used in the analysis.

Activity Monitoring (AM)

As previously reported,[14–17] the spontaneous activity of each individual dog was measured using an accelerometer.[d] Activity monitoring commenced on Day 0 and continued for the duration of the study. At each visit, the monitor was removed from the collar and placed on a telemetric reader to download the data to a personal computer.

Percent Body Weight Distribution ($\%BW_{distrib}$)

Percentage body weight distribution data were recorded for each limb using a pressure-sensitive walkway,[e] as previously described.[18,19] Ten sets of data were collected for each dog. For each data set, the mean $\%BW_{distrib}$ through each limb over a 5-second period was recorded. Data were expressed as %BW distributed to the hind or forelimbs ($\%BW_{hind–fore}$) and the % BW distributed to the index limb ($\%BW_{index}$).

Client Specific Outcome Measures

At the screening visit, specific activities that were problematic for their dog were defined in more detail and the CSOM was constructed and scored as previously described,[20] resulting in a unique set of activities for each dog. A single investigator (B.G. J. Wernham) directed each CSOM construction. After completion of the CSOM form on Day 0, the same unique set of activities was assessed at each visit.

For all subjective outcome measures, the same owner completed the assessment instrument at each visit and was not permitted to see their answers from their previous visit.

Statistical Analysis

Sex distribution, body weight, age, breed distribution (Labrador/non-Labrador), whether the impairment was predominantly fore limb or hind limb, degree of impairment, blood and urine values were all compared between the groups at D0 using appropriate statistical tests (sex, fore or hind, degree of impairment: Fisher's exact test; other variables: two-factor ANOVA with the fixed effects of group and leg [fore, hind]).

All analyses were "intent to treat" analyses. The number of dogs in each group that dropped out was compared between groups using a Chi-squared analysis.

A Kaplan–Meier survival curve was constructed to display how dogs dropped out, and a Log-rank test was performed to compare the groups. Cox proportional hazard regression was performed to test what factors were associated with dropout rate. Right-censoring (PHREG) cox proportional hazards regression analysis were performed.

Using data gathered from only the dogs that did not drop out, subjective variables (CBPI total score, CBPIt; pain score, CBPIp; interference score CBPIi, HCPI, and CSOM) and objective variables of limb use ($\%BW_{hind-fore}$, $\%BW_{index}$) were evaluated using a split-plot repeated measures ANOVA with the grouping factors of group and leg (fore/hind), and the repeat factor of time using a compound symmetry model. Day 14 data were considered baseline. Posthoc Bonferroni analysis used a P value corrected for multiple comparisons.

Activity counts for the week preceding each evaluation time point were calculated for each dog. These 7-day periods were described as "segments" (e.g, segment 1 = D7–D14; segment 8 = D105–D112). For each dog, for each day, activity counts for 6-hour periods of the day were calculated: Q1 (1200–0559 hours), Q2 (0600–11.59 hours), Q3 (1200–1759 hours), and Q4 (1800–23.59 hours). These values were averaged across the 7 days of each segment. Total weekly counts were also calculated. The activity count data were evaluated using an ANOVA in a manner, similar to that described previously. If the error were not normally distributed, the data were log transformed.

Intensity of activity was calculated by determining the percentage of minutes in each segment in which each dog had activity counts that were above that dog's upper threshold. Two upper thresholds were calculated: one for segment 1 and one for segment 2. Upper threshold was calculated by calculating the mean per minute activity value in segment 1 for each dog, and the SD. Then, the mean + 2 SDs were used to determine the "upper threshold" of activity. The percentage of minutes that activity counts were above these upper thresholds were calculated for each dog, for each segment, and these data were used for analysis as described previously.

Results

A total of 125 dogs were screened for inclusion in the study; 65 dogs were deemed eligible, were recruited, and started the study. In all, 6 of the 65 dogs dropped out from the study before D42 (first data point comparing full and reduced dose) because of reasons other than deterioration in pain control: 1 as a result of owner noncompliance (D28; RDG); 1 died (perforated gastroduodenal ulcer and heart-based hemangiosarcoma found at necropsy) (D33; RDG); 1 dog developed vestibular disease (D14; RDG); 1 as a result of undiagnosed respiratory disease (D14; RDG); 1 dog developed melena before receiving any medication (D12; MDG) and 1 because of an acutely ruptured cranial cruciate ligament (D28; MDG). Fifty-nine dogs (RDG: n = 30, MDG, n = 29) were therefore recruited and remained in the study beyond D42.

Table 2. Signalment of dogs in reduced dose group (RDG) and maintained dose group (MDG) groups.

Variable	RDG	MDG	*P* value
Sex	17 FS; 13 MC	12 FS; 17 MC	.28
Age, years (mean ± SD)	8.99 (2.63)	9.60 (3.04)	.37
Breed (Labrador/ other)	10/20	11/18	.88
Weight, kg (mean ± SD)	29.12 (9.71)	30.08 (11.21)	.84
Predominantly fore or hind limb	4 fore; 26 hind	8 fore; 21 hind	.53
High or low impairment	20 low; 10 high	17 low; 12 high	.17

FS, female spayed; M, male castrated.

There was no significant difference between the groups for sex distribution, body weight, age, breed distribution, whether the impairment was predominantly fore or hind limb, and whether the degree of impairment was high or low on D0 (Table 2). There were no significant differences between the groups in the CBC, blood chemistry, or UA values at Day 0.

Primary Outcome Measures

Significantly more dogs dropped out of the RDG (13) than the MDG (6) during the study (Chi-squared: $P = .03$, odds ratio 3.67 [1.1–12.2]. The median time for dropout in each group was 84 days, corresponding to dose reduction of 60% over the previous 2 weeks for the RDG. A Kaplan–Meier survival curve showed that dogs in the MDG dropped out at a slower rate than the RDG ($P = .035$) (Fig 1). In all, 17 of 30 dogs in the RDG completed the study, whereas 26 of 30 dogs in the RDG tolerated at least a 15% dose reduction.

Multicollinearity was not detected, but proportionality assumption testing indicated that age violated the assumption. Dividing the dogs into young and old (using 9.28 years as the breakpoint), PHREG analysis indicated that there was a significant effect of age ($P = .02$) (hazard ratio 0.56 [0.35–0.91]) on dropout rate and also an effect of group ($P = .05$) (hazard ratio 0.36 [0.13–1.01]) once age was controlled for. The chance of dropping out was approximately 3 times greater in the RDG than the MDG, and younger dogs were twice likely to drop out over time than older dogs.

Evaluating the dogs that did not drop out (n = 41), there was no overall effect of group on CBPIt (Fig 2), CBPIp, CBPIi, and HCPI (Fig 3) values. Within each group, scores were significantly lower than D14 at all evaluation time points from D28 onward for CBPIt, CBPIp, CBPIi, and HCPI scores, apart from D14 to D28 ($P = .016$), D98 ($P = .055$), and D112 ($P = .0172$) comparisons within the RDG for the HCPI, which were not significant (using posthoc Bonferroni analysis with critical *P* value set at .007).

For the $\%BW_{hind\text{-}fore}$ data, there was no overall effect of group ($P = .69$) or time ($P = .72$). For the $\%BW_{index}$ data, there was a significant effect of time ($P = .016$), but no significant effect of group ($P = .75$). $\%BW_{index}$ increased over time. Posthoc Bonferroni analysis (critical *P* value set at .007) indicated that there were significant increases in $\%BW_{index}$ between D14 and D112 ($P = .007$). Within the individual

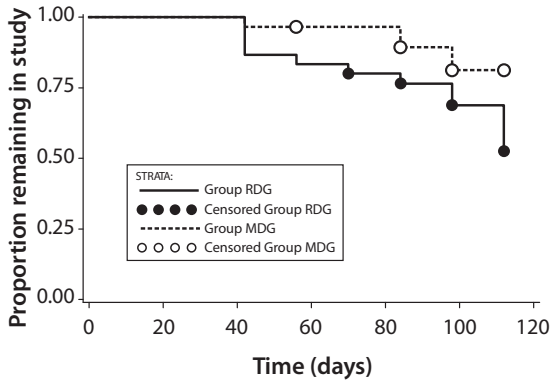

Fig 1. Kaplan–Meier plot of cumulative proportion of dogs for each group remaining in the study. Dogs in the reduced dose group (RDG) dropped out of the study at a faster rate than dogs in the maintained dose group (MDG) ($P = .035$).

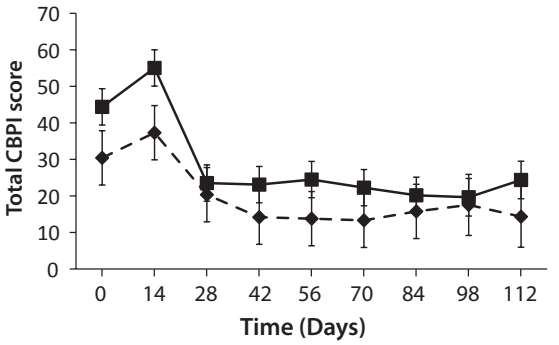

Fig 2. Total canine brief pain inventory score (CBPIt) over time for the maintenance (MDG; solid line) and reducing (RDG; dashed line) dose groups.

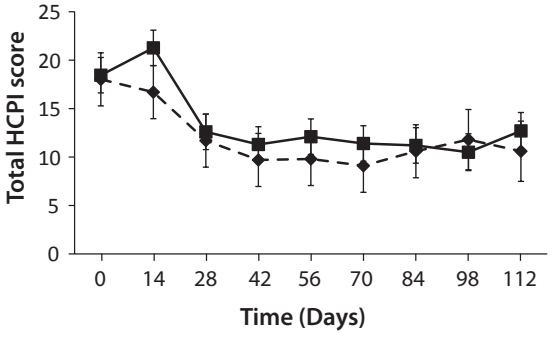

Fig 3. Helsinki Chronic Pain Index (HCPI) scores over time for the maintenance (MDG; solid line) and reducing (RDG; dashed line) dose groups.

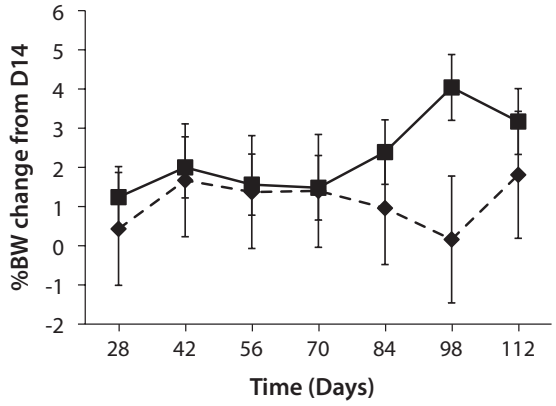

Fig 4. Change in $\%BW_{distrib}$ (index limb) compared with D14 over time for the maintenance (MDG; solid line) and reducing (RDG; dashed line) dose groups.

groups, using posthoc Bonferroni analysis (critical P value set at .007), there were no significant changes between time points for the RDG, but for the MDG, there were significant increases in $\%BW_{index}$ at D84 ($P = .004$), D98 ($P < .0001$), and D112 ($P = .0002$) compared to D14 (Fig 4).

When evaluating the total weekly activity counts, there was no effect of group ($P = .14$) or segment ($P = .74$), or any interaction of group*segment ($P = .60$). For average Q1 activity, there was a significant effect of group ($P = .032$; MDG had higher counts than RDG), but no significant effect of segment ($P = .86$), or group*segment ($P = .96$). For average Q2 activity, there was no significant effect of group ($P = .31$), segment ($P = .51$), or group*segment ($P = .50$). For average Q3 activity, there was no significant effect of group ($P = .16$) or group*segment ($P = .33$), but there was a significant effect of segment ($P = .012$). Activity increased from segment 1 to 2, and then gradually decreased over time. Posthoc Bonferroni analysis indicated that there were no significant differences between segment 1 and any other individual segments.

For average Q4 activity, there was no significant effect of group ($P = .47$) or group*segment ($P = .12$), but there was a significant effect of segment ($P = .04$). Overall, activity increased from segment 1 to 2, and then gradually decreased over time. Posthoc Bonferroni analysis indicated that there were significant increases in activity between segment 1 and segment 2 ($P = .0067$) and between segment 1 and segment 7 ($P = .0012$). Looking within the groups, there was only a significant difference (increase) between segment 1 and 6 for the MDG ($P = .0056$).

There was no evidence of an effect of group, segment, or group*segment interaction for the percentage of time above either upper threshold for activity.

Secondary Outcome Measures

CSOM. There was no effect of group on CSOM values. There was a significant effect of time, and across both groups, scores were significantly ($P < .001$) lower than time D14 at all evaluation time points from D28 onwards.

Table 3. Type of adverse events possibly associated with nonsteroidal anti-inflammatory drug administration and time of occurrence during study.

	Adverse Event	Dog Number	Group	Percent of Maintenance Dose (0.1 mg/kg) Received in the 2 Weeks prior to Signs
Day 33	Gastric perforation and death	21	RDG	85
Day 56	Vomiting	35	MDG	100
Day 70	Vomiting	38	RDG	55
Day 98	Vomiting	22	RDG	20
Day 98	Vomiting	25	MDG	100

RDG, reduced dose group; MDG maintained dose group.

Adverse Events

Of the 65 dogs that started the study, 5 dogs (RDG = 3 [4.6%], MDG = 2 [3.1%]) suffered adverse events that were likely attributable to meloxicam toxicity (Table 3). All dogs recovered without any further intervention once meloxicam was discontinued except Dog 21. This dog became acutely lethargic (no gastrointestinal adverse effects were noted by the owner before this event) and died suddenly on D33. It was discovered that this dog was inadvertently receiving a topical steroid otic medication for otitis externa concurrently with meloxicam. Gastric perforation with septic peritonitis and atrial and hepatic hemangiosarcoma was found on necropsy.

Degree of Deterioration

Of the 19 dogs that dropped out of the study because of insufficient pain control, there was a significant difference (deterioration) in CBPI, HCPI, and CSOM scores between the time of dropout and D28 (Table 4). There was no significant difference for $\%BW_{index}$ values between D28 and the time of dropout.

Discussion

This blinded, parallel group, placebo-controlled study found that, in approximately 57% of dogs, dose reduction was able to be achieved and efficacy maintained based on owner assessment, $\%BW_{distrib}$, and objectively measured activity. A median dose reduction of 60% could be achieved before owners considered their dog's pain control insufficient; 87% of dogs in the RDG tolerated at least a 15% dose reduction.

Significantly more dogs dropped out of the reducing than the MDG. The time of dropout was determined by the owner's overall assessment of their dog's pain control, and was not based on objective measures.

Table 4. The change in subjective instrument scores and objectively measured body weight distribution to the index limb between D28 and the time of drop out for dogs whose owners considered pain control insufficient.

	CSOM	CBPIt	CBPIi	CBPIp	HCPI	% BW_{index}
Mean change	1.61	18.89	10.83	6.06	5.17	0.05
SD	2.38	20.36	12.34	6.46	5.08	3.00
P value	.011	.001	.002	.001	.000	.944

CSOM, client specific outcome measures; CBPIt, total canine brief pain inventory score; CBPIi, canine brief pain inventory score for interference factors; CBPIp, canine brief pain inventory score for pain; HCPI, Helsinki Chronic Pain Index.

This should reflect what would occur in a clinical setting, where treatment alteration is often based on the owner's assessment.

It should be noted that although significantly more dogs in the RDG dropped out of the study, 6/29 dogs still dropped out of the MDG despite being maintained on a constant dose of meloxicam. Possible explanations for this include day-to-day fluctuation in the pain associated with the OA, and lack of response to the NSAID. Clinically, it is believed that dogs with OA will fluctuate between "good" and "bad" days depending on things such as the weather or degree of activity. Lack of response to NSAIDs is a recognized clinical phenomenon, but no work has evaluated how frequent this is in the dog, or what factors affect this.

To the authors' knowledge, there is only 1 study on patients evaluating maintenance and a reduced regimen of NSAID administration.[21] In that 24-week, prospective, randomized, blind, placebo-controlled study, patients were randomly assigned to receive continuous or intermittent treatment with celecoxib. The percentage of days with intake of the rescue drug used to treat flare-ups (worsening) was significantly lower ($P = .031$) in the group receiving continuous versus intermittent celecoxib.[21] It might be that in the study we report here, the reducing dose regimen resulted in more "flares" in that group, interpreted as insufficient pain control by owners.

Interestingly, these data suggested that younger dogs were approximately twice as, likely to drop out during the course of the study than older dogs. This result was surprising, as one would expect that because of assumed greater severity of disease in older dogs, they would be less tolerant of NSAID dose reduction. The expectations of owners may have been greater for the younger dogs.

We used both the HCPI and CBPI questionnaires as 2 primary outcome subjective measures. Both of these instruments have been shown to be reliable, have validity and sensitivity, and were subsequently considered the most appropriate subjective outcome measures for this study.[10,12,13]

Body weight distribution in the standing dog (%$BW_{distrib}$) measured using a pressure-sensitive walkway has been used as a measure of pain relief,[18,22] and data from other work in our laboratory indicate it to be as sensitive a measure of limb use as kinetic variables (Seibert R, Mercellin-Little DD, Roe SC, DePuy V, Lascelles BDX, unpublished data). Although %$BW_{distrib}$ appears to be a valid measure of limb use because of pain, little is known about how pain relief affects limb use in dogs with multiple limbs affected. Many of the dogs in this study had involvement of multiple limbs. This fact and the influence of learned behaviors on body carriage may have resulted in the modest changes in %$BW_{distrib}$ seen. In the MDG, there did seem to be a gradual improvement in use of the index (most severely affected) limb over time. However, it must be noted that this improvement did not reach significance until D84. These data would support the notion that long-term use of NSAIDs can result in progressive improvement over time.[2]

The accelerometer data from this study indicated that there was an increase in activity over the 2-week period of NSAID administration. This increase occurred in the afternoon and evening time periods. This confirms other investigators' findings of the effect of a short course (2 weeks) of NSAID treatment on activity in dogs with OA.[15] No investigations have been done on activity changes over time with continuous NSAID treatment. These data suggest that there is a gradual decline in activity, after the initial increase produced by the NSAID treatment. This requires further investigation.

An interesting finding of this study was that approximately 57% of dogs in the RDG were able to receive a gradually decreasing dose of NSAID over the 98-day period of dosing, with no active drug in the last 2 weeks, and the subjective and objective data suggested there was no significant deterioration. Possible explanations for this include (1) invalid outcome measures; (2) improvement because of exercise and subsequent increased muscle mass; (3) NSAID-induced changes in peripheral or central mechanisms driving pain; (4) inadequate time for dogs on low to no active drug to see a deterioration; and (5) the dogs recruited to this study were not highly enough impaired. The outcome measures may not be appropriate or sensitive enough to detect deterioration in pain control. It is possible that increased exercise in the early part of the study resulted in increased muscle mass and tone, and this effected pain relief in a way similar to how exercise has been shown to effect significant pain relief in humans.[23,24] The pain transmission system is known to be plastic, changing in response to input, and resulting in sensitization.[25] Evidence exist that COX inhibition can reverse aspects of sensitization in rodents[26] and experimentally induced hyperalgesia in humans.[27] It is possible that medication with an NSAID, in some dogs, resulted in downregulation of peripheral sensitization, central sensitization, or both, resulting in a reduction in pain and allowing the drug to be reduced to zero without loss of efficacy. No studies on the effect of NSAIDs on sensitization in dogs have been

performed. It is possible that a longer study would have detected deterioration in these dogs as a result of "resensitization," or flare up of peripheral drivers of pain. The dogs recruited to this study were all suffering from OA-related pain and impairment, and represent the typical cases presenting to our clinic for treatment. Further studies should be performed to evaluate dose reduction in the most highly impaired cases seen in practice.

The incidence of adverse events that were probably associated with meloxicam was low (7.6% of dogs) and comparable to previous reports.[6,9] This study was not powered to look at differences between groups for adverse effects. The dog that died while on the study did not show any other gastrointestinal signs before becoming acutely lethargic and dying several hours later. It is uncertain whether the administration of a topical steroid otic medication for otitis externa concurrently with meloxicam and the diagnosis of atrial and hepatic hemagiosarcoma contributed to the dog's sudden deterioration and death.

In conclusion, it appears that gradual dose reduction of meloxicam can be performed, and pain relief and activity can be maintained. However, whether this can be successfully performed appears to depend on the individual dog. The current study did not investigate what factors might predict a successful response to gradual dose reduction of an NSAID. The optimal way of performing dose reduction or how quickly dose reduction should be performed remains unknown. Further clinical research is warranted to understand how dose reduction down to zero can be achieved in chronically painful disease.

Footnotes

[a] Canon Medical CXDI-50G Sensor, Eklin Medical Systems, Santa Clara, CA
[b] Metacam 1.5 mg/mL Oral Solution, Boehringer Ingelheim Vetmedica, Inc, St Joseph, MO
[c] Methylcellulose (Ora Plus) opacifier, and coloring (McCormick Food Colors Yellow and Blue), Sparks, MD
[d] Actical Activity Monitor, Philips Respironics Co, Bend, OR
[e] 7100 QL Virtual Sensor 4 Mat System, Tekscan, Boston, MA

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Conflict of Interest: Dr Lascelles performs continuing education lectures sponsored by Boehringer Ingelheim Vetmedica Inc, and has acted as a consultant to Boehringer Ingelheim Vetmedica Inc. Dr Lascelles has been a member of advisory boards. Dr Wernham received an honorarium from the sponsor, Boehringer Ingelheim Vetmedica Inc, to help cover travel expenses to present the data at a scientific meeting.

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