Evaluation of tramadol for treatment of osteoarthritis in geriatric cats

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OBJECTIVE
To evaluate tramadol for treatment of signs of pain and impaired mobility in geriatric cats with osteoarthritis.

DESIGN
Randomized controlled crossover trial.

ANIMALS
24 client-owned geriatric (≥ 10 years old) cats with osteoarthritis.

PROCEDURES
Otherwise healthy cats with owner-identified mobility impairment and clinical and radiographic evidence of osteoarthritis involving at least 1 appendicular joint were enrolled in the study. Cats were treated with tramadol orally at dosages of 0 (placebo), 1, 2, and 4 mg/kg (0, 0.45, 0.9, and 1.8 mg/lb) twice a day for 5 days, with a 2-day (weekend) washout period between treatments. Mobility was assessed with a collar-mounted activity monitor system, and impairments in activity were assessed with a client-completed questionnaire.

RESULTS
17 cats completed the study; 7 cats were withdrawn. There was a significant increase in activity with the 2-mg/kg dosage of tramadol, compared with activity when cats received the placebo. Significantly more owners (11/18) considered their cats to have improved with the 2-mg/kg treatment, compared with all other dosages (6/19 to 8/21). Most owners (17/20 [85%]) considered their cat's global quality of life to have improved during the study. Adverse events, predominantly euphoria, dysphoria, sedation, decreased appetite, and diarrhea, were significantly more frequent with the 4-mg/kg (8/19) and 2-mg/kg (6/18) treatments but not with the 1-mg/kg (2/21) treatment, compared with frequency of adverse events with the placebo (0/21).

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested a beneficial effect of twice-daily oral administration of tramadol at a dosage of 2 mg/kg in geriatric cats with osteoarthritis. Adverse events were dose dependent, and caution should be exercised in cats that have concurrent disease or are receiving other drugs that may produce adverse gastrointestinal effects. (*J Am Vet Med Assoc* 2018;252:565–571)

Osteoarthritis is an important clinical problem in cats, particularly in older animals, and can be associated with pain and mobility impairment.[1–7] Effective and safe analgesics for long-term use in cats continue to be an unmet medical need. Although NSAIDs can produce pain relief and improve mobility in cats with osteoarthritis,[8–10] they are not approved for long-term use in cats in the United States and can cause serious adverse effects.[9,11,12] Adverse effects are especially concerning in geriatric cats because of an increased likelihood of comorbidities.[13,14]

Tramadol, a synthetic opioid, has multiple mechanisms of action[15–18] and relatively high bioavailability and slow clearance in cats, compared with other species,[19–21] and produces thermal antinociception in cats.[22] There is increasing evidence that osteoarthritis may involve a complex pain state with nociceptive, inflammatory, and neuropathic components,[23,24] and in cats, it is associated with central hyperalgesia.[7] In horses with laminitis, a painful disease with inflammatory and neuropathic components with clinical signs suggestive of hyperalgesia,[25] oral administration of tramadol produced indicators of pain relief, including significant reductions in weight shifting, with detectable albeit statistically insignificant decreases in plasma tumor necrosis factor-α concentrations.[26,27] This proinflammatory cytokine is intricately involved in the pathophysiology of osteoarthritis, neuropathic pain, and hyperalgesia.[28–31] In human patients with neuropathic pain, tramadol has been reported[18] to

ABBREVIATIONS
CSOM Client-specific outcome measures

significantly decrease the concentration of plasma tumor necrosis factor-α, and it can be effective in the management of painful osteoarthritis.[32,33] Together, these data suggest that tramadol might be useful for managing the complex pain associated with osteoarthritis in cats.

Although tramadol is commonly prescribed for chronic pain in cats and dogs, there is no published research evaluating its use for this purpose in these species.[34] Therefore, the objective of the study reported here was to investigate the use of tramadol in geriatric cats with osteoarthritis. Our hypothesis was that tramadol would produce dose-dependent improvement in measures of mobility and pain in affected cats.

Materials and Methods

Animals and inclusion criteria

Participation in the study was voluntary, and written owner informed consent was obtained prior to enrollment. The University of California-Davis Veterinary Medical Teaching Hospital Clinical Trial Review Board reviewed and approved the study protocol.

Geriatric (≥ 10 years old) cats of either sex with owner-identified mobility impairment were recruited. Cats were evaluated with general physical, orthopedic, and neurologic examinations; a CBC; and serum biochemical analyses. Orthogonal radiographic views were obtained of joints for which manipulation elicited an aversive response during physical examination or for which there were signs of adjacent muscle atrophy. Cats were included in the study if all the following criteria were met: the owners had noticed decreased patient mobility, the cat had radiographic evidence of osteoarthritis involving at least 1 synovial appendicular joint, the cat was indoor only, and the owners had a stable routine of daily living during the study period.

Exclusion criteria

Cats were excluded from the study if there was any detectable systemic disease, if there were any clinically important abnormalities on laboratory tests, or if they were receiving any NSAIDS, other analgesic medications, glucosamine-chondroitin sulfate supplements, or similar products (eg, chondroprotectants) at the time of assessment for study eligibility. In addition, cats were dropped from the study if inclusion criteria were violated at any point during the study, if they developed frequent or serious adverse effects, or if they missed > 1 study treatment (ie, tramadol administration)/wk. Owners were allowed to drop out of the study at any time of their own volition.

Drug preparation and study design

Tramadol tablets[a] (50 mg) were crushed into powder and placed into identical-looking capsules corresponding to doses of 0 mg/kg (0 mg/lb), 1 mg/kg (0.45 mg/lb), 2 mg/kg (0.9 mg/lb), or 4 mg/kg (1.8 mg/lb) of body weight for each individual cat. For the placebo treatment, sucrose (approx 45 mg total) was used instead of tramadol. Owners were blinded to treatment allocation, and a complete Latin square design with a washout period of 2 days between each treatment was used. Cats were treated with tramadol or placebo every 12 hours on weekdays (Monday through Friday). No medication was administered on weekends (Saturday and Sunday). Owners had the choice to insert the capsule into a pill pocket[b] to facilitate oral administration.

Outcome measurements

For each cat, measured outcomes included activity level and changes in 3 owner-selected place- and time-specific impaired activities. Activity was assessed with the use of a collar-mounted activity monitor system[c] as previously reported.[10,35] Changes in the owner-selected impaired activities, which were considered a priori the primary outcome measure, were assessed with a CSOM questionnaire as described previously.[10] Briefly, owners rated the changes in their cat's impaired activities in relation to 2 time periods: "relative to the preceding weekend" and "relative to when the cat was normal." On day 0 of the study, the cats were fitted with the activity monitor device, and the first CSOM questionnaire was answered. Subsequently, 1 week (week 1) was allowed for acclimatization, and on day 7, baseline assessments of activity level and the CSOM were obtained. Subsequent assessments occurred on day 14 (week 2), day 21 (week 3), day 28 (week 4), and day 35 (week 5). Owners were instructed on use of the questionnaire prior to each assessment. Blood was collected for CBC and serum biochemical analysis at the end of week 5. At this time, owners also responded to the global quality-of-life questionnaire that asked whether their cat's quality of life had deteriorated during the study, was the same as before the study, or had improved, compared with quality of life before the study. Adverse events were recorded throughout the study.

Statistical analysis

Statistical analyses were performed with commercial statistical software.[d] Data were tested for normality with the D'Agostino-Pearson omnibus normality test. Continuous nonnormally distributed data were log-transformed. Accordingly, activity counts were analyzed with 2-way repeated-measures ANOVA and Bonferroni posttest. The areas under the curve for the total activity counts for each treatment were calculated with the trapezoidal method, log-transformed, and compared with a repeated-measures ANOVA followed by the Bonferroni posttest. The scores for each CSOM (ie, CSOM "relative to preceding weekend" and CSOM "relative to when the cat was normal") were analyzed with the

Friedman test followed by the Dunn posttest. The frequency distributions for CSOM "relative to preceding weekend" were calculated and compared by means of χ^2 tests. Adverse event data were analyzed with χ^2 tests. Data were summarized and expressed as mean ± SD, unless otherwise indicated. Values of $P \leq 0.05$ were considered significant.

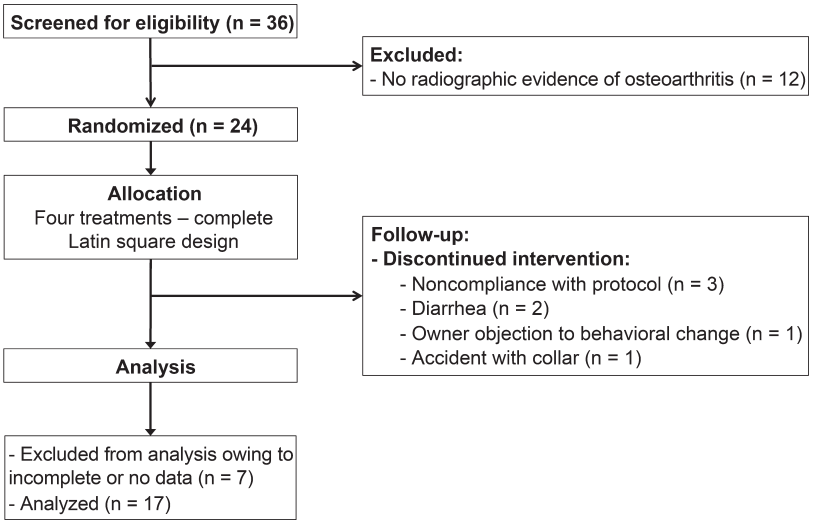

Figure 1—Flow diagram for a study designed to evaluate tramadol (0, 1, 2, and 4 mg/kg [0, 0.45, 0.9, and 1.8 mg/lb]) given orally every 12 hours on measures of mobility and activity in geriatric cats (≥ 10 years old) with osteoarthritis. Treatments were given in random order during 5 consecutive weekdays with a 2-day washout period (weekend) between treatments. Activity counts obtained with an activity-monitoring device and a CSOM questionnaire were used to assess outcomes for each treatment.

Results

Animals

Thirty-six cats were evaluated for inclusion in the study, with 24 fulfilling inclusion criteria and enrolled (14 spayed females, 10 neutered males; **Figure 1**). Two of the enrolled cats belonged to the same owner but were studied on separate occasions. None of the enrolled cats had received analgesic or anti-inflammatory medications or both for at least 2 months before the study, and none had received chondroprotectants within the previous year. Cats included domestic shorthairs (n = 14), domestic longhairs (5), and a Siamese, Persian, Manx, Birman, and Bengal crossbred. Overall median age and body weight were 13 years (range, 10 to 21 years) and 4.8 kg (10.6 lb; range, 2.5 to 7.4 kg [5.5 to 16.3 lb]). Median age and body weight of females and males were 13 years (range, 10 to 21 years) and 13 years (range, 12 to 17 years), respectively, and 4.1 kg (9.0 lb; range, 2.5 to 6.8 kg [5.5 to 15 lb]) and 6.2 kg (13.6 lb; range, 3.2 to 7.4 kg [7 to 16.3 lb]), respectively. All cats had been gonadectomized long before the study, although owners were not queried on the precise time when this was performed.

In total, 59 joints (24 hip, 17 stifle, 15 elbow, 1 shoulder, 1 carpal, and 1 tarsal joints) had radiographic evidence of osteoarthritis. No attempt was made to diagnose all possible affected joints. Multiple joints (range, 2 to 4) were documented as affected in 20 of the enrolled cats. Seventeen cats completed the study in its entirety; 7 cats were withdrawn at various times during the study. Reasons included cat refusal to take medications (n = 3), diarrhea (2), accident with collar-mounted activity monitor system (1), and owner objection to behavioral change (1). The number of cats that completed at least 1 treatment was 21, 21, 18, and 19, respectively, for the 0-, 1-, 2-, and 4-mg/kg treatments.

Activity counts

Data for activity counts and CSOM were summarized **(Figure 2)**. Mean ± SD activity counts ($\times 10^3$) during treatment (Monday through Friday) were 530 ± 24 (n = 21), 562 ± 34 (21), 629 ± 99 (18), and 557 ± 104 (19) for the 0-, 1-, 2-, and 4-mg/kg treatments, respectively. Corresponding coefficients of variation during each treatment were 4.5%, 6.1%, 15.7%, and 18.72%. The area under the curve for activity counts for the 2-mg/kg treatment was significantly greater than that of the placebo.

Owner-assessed outcomes

Analyses of the CSOM "relative to the preceding weekend" considering all subcategories of improved (slightly, moderately, and very) did not reveal significant differences among treatments. Simplifying the categories to "improved," "same," and "worse" revealed that significantly more owners reported their cats as "improved" with the 2-mg/kg treatment, compared with all other treatments **(Figure 3)**. Analyses of the CSOM "relative to when the cat was normal" did not reveal any significant treatment effect. Of 20 owners who assessed the global quality of life at the end of the trial, 17 (85%) responded that global quality of life had improved during the study, 2 responded that it was the same as before the study, and 1 responded that it had deteriorated, compared with quality of life before the study.

Adverse events

Adverse events were noted in 14 of 20 cats; 2 of these cats had adverse events during 2 separate treatments (total of 16 adverse events). No adverse events were reported for the placebo treatment. Adverse events were most common with the 4-mg/kg (n = 8/19) treatment, followed by the 2-mg/kg (6/18) and 1-mg/kg (2/2]) treatments, and compared with the placebo, adverse events were significantly more common with the 2- and 4-mg/kg treatments but not with the 1-mg/kg treatment. Comparisons between

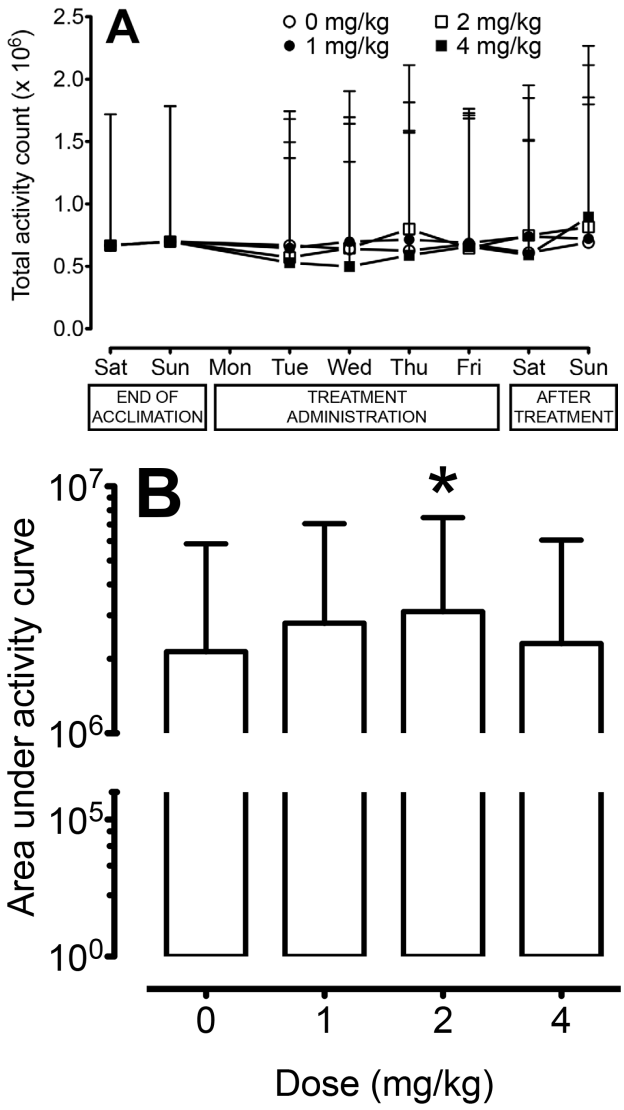

Figure 2—Effects of tramadol given orally at a dosage of 0 (placebo), 1, 2, and 4 mg/kg every 12 hours for 5 days on measures of mobility and activity in geriatric cats (n = 17) with osteoarthritis in a crossover study. A—Daily mean ± SD activity counts before (end of acclimation), during, and after treatments. B—Calculated mean ± SD area under the curve of activity counts (counts • time) during each treatment. An asterisk indicates significant ($P < 0.05$) difference relative to placebo.

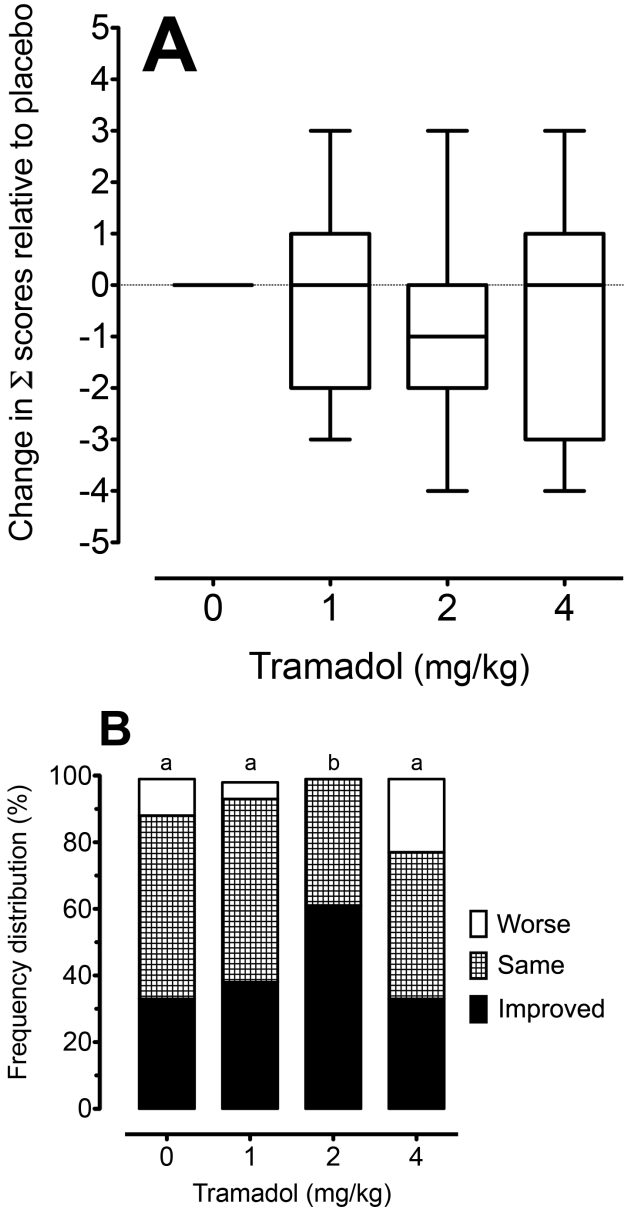

Figure 3—Effects of tramadol given orally at a dosage of 0 (placebo), 1, 2, and 4 mg/kg every 12 hours for 5 days on measures of mobility and activity in geriatric cats (n = 17) with osteoarthritis in a crossover study. A—Box-and-whisker plots of changes in the sum of owner-reported scores for impaired activities, "relative to when the cat was normal." For each plot, the box represents the 25th and 75th percentiles, the line within each box represents the median, and the whiskers represent the range. B—Frequency distribution (%) of changes in mobility scores reported by the owners, "relative to the weekend preceding each respective treatment." Treatments without common superscript letters were significantly ($P < 0.05$) different.

the 1-, 2-, and 4-mg/kg treatments revealed no significant differences in frequency of adverse events. Opioid-like adverse effects (eg, mydriasis, euphoria, agitation or restlessness, sedation, and hiding) and adverse gastrointestinal effects (eg, decreased appetite and diarrhea) were the most common. In 1 cat, the activity monitor collar became accidentally lodged in the cat's mouth during the acclimation week, and the owner opted to drop out of the study. Treatment order and additional details associated with each adverse event were summarized (**Supplementary Table S1**, available at avmajournals.avma.org/doi/suppl/10.2460/javma.252.5.565).

Discussion

The present study investigated the use of tramadol, a drug with a multimodal mechanism of action,[15–18] in geriatric cats with osteoarthritis, a multifaceted painful condition involving nociceptive, inflammatory, and neuropathic components[23,24] and associated with

central sensitization, hyperalgesia, and allodynia.[7,36,37] In horses with chronic laminitis, a similarly complex painful condition,[25] tramadol produces measurable analgesic effects.[26,27] This is consistent with results of the present study, in which there was a significant increase in activity level for cats receiving the 2-mg/kg treatment, compared with the activity level for all other treatments. Furthermore, most owners (17/20 [85%]) reported that their cats' global quality of life improved during the study. We were unable to confirm our hypothesis of a dose-dependent improvement with tramadol administration; nonetheless, the results suggested that oral tramadol administration twice daily at a dosage of 2 mg/kg generally had a beneficial effect in geriatric cats with osteoarthritis and mobility impairment.

The improved activity with tramadol treatment in the present study could have resulted from a normalizing effect on central sensitization,[1,7,38] possibly via modulation of production of proinflammatory cytokines such as tumor necrosis factor-α, or by means of any other of its multiple mechanisms of action.[18,26,28–31] Activity monitor data should be interpreted cautiously because tramadol also caused behavioral changes that could have altered activity irrespective of pain relief. In experimental studies[19,22] of cats, tramadol caused euphoria (ie, cats were playful or kneading) for several hours. In the present study, individual owners reported behaviors that could be construed as dysphoric (panicky, hiding all the time, agitated or restless, or climbing up to unusual places), euphoric (more snuggly or friendly or seeking human interaction more frequently), or sedated and dissociated (staring into space for long periods of time, disinterested in human interaction, or "stoned"). To our knowledge, most of these behaviors have not been reported previously with administration of tramadol in cats,[5,19,22,38] and they could have variable effects on activity level. The variability in activity monitor counts increased dependent on tramadol dosage and was 3 times as high with the 2- and 4-mg/kg treatments, compared with variability with the placebo. Thus, tramadol and likely other centrally acting drugs may change activity level in cats in ways that could affect the use of activity monitoring as an index of pain relief. This notion is consistent with findings of a recent study[38] that indicated meloxicam alone produced a significant increase in activity counts, with no significant increase when meloxicam was combined with tramadol (3 mg/kg [1.36 mg/lb]). Focusing on owner assessments, with the use of proper controls, may be a more robust measure of outcome. In the present study, the improved activity with the 2-mg/kg treatment versus placebo corroborated the finding that significantly more owners identified a positive effect with this treatment.

Osteoarthritis is very common in geriatric cats, affecting up to 90% of studied populations.[2,3,6] It is a common cause of pain and discomfort, affecting both the cat's quality of life and the human-cat bond.[4,6,39] Tramadol-induced behaviors such as playfulness and kneading[19,22] were expected to positively affect the human-animal bond and favor a positive owner perception. This notion appears to have been supported by the results of the quality of life assessment and the CSOM "relative to the preceding weekend" for the 2-mg/kg treatment. However, tramadol also caused disruptive behaviors that bothered some owners and produced additional adverse effects even with the lower dosages. Thus, results of the present study may be useful in guiding initial dosage selection, but this dosage may need to be further refined according to individual patient needs. In cats for which a balance between efficacy and tolerability cannot be reached with appropriate dosage adjustments or when owners object to adverse effects, an alternative analgesic regimen may need to be considered.

The results of the CSOM "relative to when the cat was normal" did not yield any significant treatment effect in the present study. Although we did not attempt to define the precise duration of mobility impairment, it was present for several years in some cats, at times back to when they were not considered geriatric as defined for this study. As there certainly are musculoskeletal changes associated with age alone as well as with osteoarthritis, it would be unreasonable to expect that these cats would become "normal" with treatment. Also, this outcome variable relied heavily on owners' long-term memory of their "normal" cat. As such, interpretation of these results should be tempered by these considerations. A decrease in total score with the 2-mg/kg treatment relative to placebo, producing a negative median value, indicated that this dosage favored a greater ability to perform the previously impaired activities. Although not statistically significant, this result was consistent with those obtained with the CSOM "relative to the preceding weekend" and the activity counts.

Dose-dependent adverse effects were noted in the present study, in agreement with previous reports in nongeriatric cats[22] and human patients.[40] Adverse effects most frequently affected the gastrointestinal system or CNS. This was in agreement with results of a recent study[38] in geriatric cats treated orally with tramadol (3 mg/kg) and meloxicam for 25 days. It was also qualitatively comparable to reports of human patients[15,40,41] but somewhat different from results described in healthy younger cats[22] in which there were adverse CNS effects but no adverse gastrointestinal effects. In a group of 8 cats treated orally with tramadol and meloxicam for 25 days, 5 developed adverse effects.[38] Oral administration of tramadol at 5 or 10 mg/kg (2.27 or 4.5 mg/lb) twice daily for 7 days produced no adverse events in horses with laminitis.[26,27] One nonlaminitic horse developed mild colic while being medicated with tramadol orally at a dosage of 10 mg/kg twice daily for 5 days in a separate study.[21] These similarities and differences in adverse effects may be due to cats' limited ability to produce and glucuronidate *O*-desmethyl tramadol[19] relative to humans[15,41] and horses.[21,27] The occurrence of adverse gastrointestinal effects in the present and in another

long-term study in geriatric cats[38] but not in a previous single-dose study in nongeriatric cats[22] may relate to longer duration of exposure to tramadol, to pharmacological differences between geriatric and nongeriatric cats, or to other factors. It is unlikely to be related to cyclooxygenase products because tramadol does not inhibit prostanoid formation.[42]

It is not known whether adverse effects would become more frequent with more prolonged administration than in the present study. In studies of human patients, adverse effects were more common initially and generally decreased over time.[40] Discontinuation due to adverse events was also more common early in treatment versus during maintenance.[40] The design of the present study did not allow for evaluation of temporal patterns of adverse events. Future studies are indicated. Given the somewhat frequent occurrence of adverse events in the geriatric cats of the present study, the risks versus benefits of using tramadol for pain management of osteoarthritic geriatric cats should be carefully considered. Principles of multimodal therapy, including the use of nonpharmacological modalities, to minimize drug- and dose-related adverse effects should be given strong consideration. If tramadol is to be used, the goal should be to use the lowest effective dose possible to maximize efficacy in relation of adverse effects. This will require individualized patient evaluation and therapy.

The pharmacokinetics of tramadol during repeated oral administrations has not been reported in cats. In horses, which glucuronidate *O*-desmethyl tramadol very efficiently, dose-dependent accumulation was documented for both tramadol and *O*-desmethyl tramadol over a 5-day administration period.[21] Accumulation is also a possibility in the geriatric cats of the present study given the cats' limitations for glucuronidation, although it is not known whether glucuronide conjugation is important for tramadol metabolism in cats. There also are no reports on the pharmacokinetics of tramadol in geriatric cats. In elderly human patients, dose adjustment may be required because the elimination half-life is increased.[15,40] Similar phenomena may occur in geriatric cats, but this possibility would require verification with a controlled study. Despite these considerations, enough drug clearance should occur within the 2-day washout period between treatments,[19] and carryover effect was not important, as indicated by the finding of no significant day effect in the 2-way repeated-measures ANOVA.

A challenge encountered in the present investigation was that some owners had difficulty in identifying 3 impaired activities in their cats or would list activities that fulfilled the study criteria established a priori but that were probably difficult to be reversed unless the treatment had very robust effects. For example, tramadol would be unlikely to reverse a severely impaired ability to jump from the floor onto the kitchen counter in the morning. These issues may explain the relative discrepancy between the overall highly positive treatment effects on the global quality of life, compared with the other outcomes. Focusing on 1 main activity that could be reasonably expected to change and inquiring about the global quality of life at the end of each treatment, instead of only once at the end of the study, might have been a better approach.

At present, there is no gold-standard toolset for evaluation of chronic pain and response to analgesic treatment in cats. Changes in mobility assessed subjectively with CSOM or objectively via accelerometers have been commonly used for this purpose[10,37,38] and were the approach selected in the present study. The ability of the CSOM to identify treatment effects with meloxicam, compared with a placebo, has been somewhat inconsistent.[10,43] In one of these studies, the CSOM did not detect significant changes during treatment but detected significant changes, presumably because of recurrence of clinical signs, after treatment was discontinued, compared with the placebo.[43] By comparison, accelerometer-based activity assessments correlate well with distance moved[35] and have more consistently detected treatment effects.[10,37,38] Both modalities were able to identify a significant treatment effect in the present study. Other objective evaluation modalities exist, including ground reaction forces,[37] mechanical paw withdrawal thresholds,[37] positron emission tomography,[36] and goniometry,[44] but they were not available to us in the present study.

In conclusion, this study was designed to gain insight into the usefulness of tramadol for treating osteoarthritis pain in geriatric cats. The results showed that twice-daily oral administration of tramadol at a dosage of 2 mg/kg produced detectable improvements in measures of mobility in these cats, with a positive impact on cats' quality of life according to owners. Clinically, because there were dose-dependent adverse events, most frequently manifested as behavioral changes, decreased appetite, and diarrhea, additional dosage refinement may be necessary in individual cats, aiming to balance efficacy and tolerability. Caution should be exercised if tramadol is used concomitantly with drugs that also cause adverse gastrointestinal effects.

Acknowledgments

Supported by the Center for Companion Animal Health, School of Veterinary Medicine, University of California-Davis.

The authors thank Drs. Neil Willits and Aaron Rendahl for assistance with study design and statistical analyses and Dr. Grace Monmaney, Sarah Sanders, Jessica Villanueva, Briana Hammamoto, Teresa Hayes, and Chrissy Kinkade for technical assistance.

Footnotes

a. Tramadol HCl tablets, Teva Pharmaceutical Industries Ltd, Sellersville, Pa.
b. Feline Greenies Pill Pockets (salmon flavor), The Nutro Co, Franklin, Tenn.
c. Actical Mini Mitter, Phillips Respironics, Bend, Ore.
d. Prism, version 5.0c for MAC OS, GraphPad Software Inc, San Diego, Calif.

References

1. Kerwin SC. Osteoarthritis in cats. *Top Companion Anim Med* 2010;25:218–223.
2. Fox SM, Robertson SA, Tranquilli WJ, et al. Pathophysiology of osteoarthritic pain. In: Fox SM, ed. *Chronic pain in small animal medicine*. London: Manson Publishing Ltd, 2010;74–96.
3. Hardie EM, Roe SC, Martin FR. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994–1997). *J Am Vet Med Assoc* 2002;220:628–632.
4. Lascelles BD, Henry JB III, Brown J, et al. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Vet Surg* 2010;39:535–544.
5. Lascelles BD, Robertson SA. DJD-associated pain in cats: what can we do to promote patient comfort? *J Feline Med Surg* 2010;12:200–212.
6. Stamper C. Osteoarthritis in cats: a more common disease than you might expect. *FDA Vet Newsl* 2008;23(2):6–8.
7. Guillot M, Taylor PM, Rialland P, et al. Evoked temporal summation in cats to highlight central sensitization related to osteoarthritis-associated chronic pain: a preliminary study (Erratum published in *PLoS One* 2014;9:e114659). *PLoS One* 2014;9:e97347.
8. Gunew MN, Menrath VH, Marshall RD. Long-term safety, efficacy and palatability of oral meloxicam at 0.01–0.03 mg/kg for treatment of osteoarthritic pain in cats. *J Feline Med Surg* 2008;10:235–241.
9. Lascelles BD, Court MH, Hardie EM, et al. Nonsteroidal anti-inflammatory drugs in cats: a review. *Vet Anaesth Analg* 2007;34:228–250.
10. Lascelles BD, Hansen BD, Roe S, et al. Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *J Vet Intern Med* 2007;21:410–416.
11. Gunn-Moore D. NSAIDs and cats—it's been a long journey. *J Feline Med Surg* 2010;12:519.
12. Jones RS. Nonsteroidal anti-inflammatory drugs in the cat (Erratum published in *Vet Anaesth Analg* 2007;34:450). *Vet Anaesth Analg* 2007;34:225–227.
13. Gaynor JS. Other drugs used to treat pain. In: Gaynor JS, Muir WW, eds. *Handbook of veterinary pain management*. 2nd ed. St Louis: Mosby Inc, 2009;260–276.
14. Fox SM, Robertson SA, Tranquilli WJ, et al. Pharmacologics (drug classes). In: Fox SM, ed. *Chronic pain in small animal medicine*. London: Manson Publishing Ltd, 2010;113–137.
15. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000;60:139–176.
16. Bianchi M, Martucci C, Ferrario P, et al. Increased tumor necrosis factor-α and prostaglandin E_2 concentrations in the cerebrospinal fluid of rats with inflammatory hyperalgesia: the effects of analgesic drugs. *Anesth Analg* 2007;104:949–954.
17. Bianchi M, Rossoni G, Sacerdote P, et al. Effects of tramadol on experimental inflammation. *Fundam Clin Pharmacol* 1999;13:220–225.
18. Kraychete DC, Sakata RK, Issy AM, et al. Proinflammatory cytokines in patients with neuropathic pain treated with tramadol. *Rev Bras Anestesiol* 2009;59:297–303.
19. Pypendop BH, Ilkiw JE. Pharmacokinetics of tramadol, and its metabolite *O*-desmethyl-tramadol, in cats. *J Vet Pharmacol Ther* 2008;31:52–59.
20. KuKanich B, Papich MG. Pharmacokinetics of tramadol and the metabolite *O*-desmethyltramadol in dogs. *J Vet Pharmacol Ther* 2004;27:239–246.
21. Guedes AG, Knych HK, Soares JH, et al. Pharmacokinetics and physiological effects of repeated oral administrations of tramadol in horses. *J Vet Pharmacol Ther* 2014;37:269–278.
22. Pypendop BH, Siao KT, Ilkiw JE. Effects of tramadol hydrochloride on the thermal threshold in cats. *Am J Vet Res* 2009;70:1465–1470.
23. Schaible HG. Mechanisms of chronic pain in osteoarthritis. *Curr Rheumatol Rep* 2012;14:549–556.
24. Ohtori S, Orita S, Yamashita M, et al. Existence of a neuropathic pain component in patients with osteoarthritis of the knee. *Yonsei Med J* 2012;53:801–805.
25. Jones E, Vinuela-Fernandez I, Eager RA, et al. Neuropathic changes in equine laminitis pain. *Pain* 2007;132:321–331.
26. Guedes AG, Matthews NS, Hood DM. Effect of ketamine hydrochloride on the analgesic effects of tramadol hydrochloride in horses with signs of chronic laminitis-associated pain. *Am J Vet Res* 2012;73:610–619.
27. Guedes A, Knych H, Hood D. Plasma concentrations, analgesic and physiologic assessments in horses with chronic laminitis treated with two doses of oral tramadol. *Equine Vet J* 2016;48:528–531.
28. Lee AS, Ellman MB, Yan D, et al. A current review of molecular mechanisms regarding osteoarthritis and pain. *Gene* 2013;527:440–447.
29. Penninx BW, Abbas H, Ambrosius W, et al. Inflammatory markers and physical function among older adults with knee osteoarthritis. *J Rheumatol* 2004;31:2027–2031.
30. Orita S, Koshi T, Mitsuka T, et al. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. *BMC Musculoskelet Disord* 2011;12:144.
31. Junger H, Sorkin LS. Nociceptive and inflammatory effects of subcutaneous TNFalpha. *Pain* 2000;85:145–151.
32. DeLemos BP, Xiang J, Benson C, et al. Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. *Am J Ther* 2011;18:216–226.
33. Manchikanti L, Ailinani H, Koyyalagunta D, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician* 2011;14:91–121.
34. Grubb T. What do we really know about the drugs we use to treat chronic pain? *Top Companion Anim Med* 2010;25:10–19.
35. Lascelles BD, Hansen BD, Thomson A, et al. Evaluation of a digitally integrated accelerometer-based activity monitor for the measurement of activity in cats. *Vet Anaesth Analg* 2008;35:173–183.
36. Guillot M, Chartrand G, Chav R, et al. [^{18}F]-fluorodeoxyglucose positron emission tomography of the cat brain: a feasibility study to investigate osteoarthritis-associated pain. *Vet J* 2015;204:299–303.
37. Guillot M, Moreau M, Heit M, et al. Characterization of osteoarthritis in cats and meloxicam efficacy using objective chronic pain evaluation tools. *Vet J* 2013;196:360–367.
38. Monteiro BP, Klinck MP, Moreau M, et al. Analgesic efficacy of an oral transmucosal spray formulation of meloxicam alone or in combination with tramadol in cats with naturally occurring osteoarthritis. *Vet Anaesth Analg* 2016;43:643–651.
39. Sparkes AH, Heiene R, Lascelles BD, et al. ISFM and AAFP consensus guidelines: long-term use of NSAIDs in cats. *J Feline Med Surg* 2010;12:521–538.
40. Langley PC, Patkar AD, Boswell KA, et al. Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain. *Curr Med Res Opin* 2010;26:239–251.
41. Cossmann M, Kohnen C, Langford R, et al. Tolerance et securite d'emploi du tramadol: resultats des etudes internationales et donnees de la pharmacovigilance. *Drugs* 1997;53(suppl 2):50–62.
42. Buccellati C, Sala A, Ballerio R, et al. Tramadol antiinflammatory activity is not related to a direct inhibitory action on prostaglandin endoperoxide synthases. *Eur J Pain* 2000;4:413–415.
43. Gruen ME, Griffith E, Thomson A, et al. Detection of clinically relevant pain relief in cats with degenerative joint disease associated pain. *J Vet Intern Med* 2014;28:346–350.
44. Lascelles BD, Dong YH, Marcellin-Little DJ, et al. Relationship of orthopedic examination, goniometric measurements, and radiographic signs of degenerative joint disease in cats. *BMC Vet Res* 2012;8:10.