Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis

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OBJECTIVE
To investigate the effectiveness of tramadol for treatment of osteoarthritis in dogs.

DESIGN
Randomized, blinded, placebo-controlled crossover study.

ANIMALS
40 dogs with clinical osteoarthritis of the elbow or stifle joint.

PROCEDURES
Dogs orally received 3 times/d (morning, midday, and night) for a 10-day period each of 3 identically appearing treatments (placebo; carprofen at 2.2 mg/kg [1 mg/lb], q 12 h [morning and night], with placebo at midday; or tramadol hydrochloride at 5 mg/kg [2.3 mg/lb], q 8 h) in random order, with treatment sessions separated by a minimum 7-day washout period. Vertical ground reaction forces (vertical impulse [VI] and peak vertical force [PVF]) were measured and Canine Brief Pain Inventory (CBPI) scores assigned prior to (baseline) and at the end of each treatment period. Repeated-measures ANOVA was performed to compare VI and PVF data among and within treatments, and the χ² test was used to compare proportions of dogs with a CBPI-defined positive response to treatment.

RESULTS
35 dogs completed the study. No significant changes from baseline in VI and PVF were identified for placebo and tramadol treatments; however, these values increased significantly with carprofen treatment. Changes from baseline in VI and PVF values were significantly greater with carprofen versus placebo or tramadol treatment. A significant improvement from baseline in CBPI scores was identified with carprofen treatment but not placebo or tramadol treatment.

CONCLUSIONS AND CLINICAL RELEVANCE
10 days of treatment with tramadol as administered (5 mg/kg, PO, q 8 h) provided no clinical benefit for dogs with osteoarthritis of the elbow or stifle joint. (J Am Vet Med Assoc 2018;252:427–432)

Osteoarthritis is a common condition that affects > 20% of the adult dog population, or approximately 14 million adult dogs in the United States.1–2 Tramadol, a weak μ-opoid receptor agonist that facilitates the descending serotonergic system (by inhibition of the reuptake of noradrenaline and serotonin in nerve endings), is commonly used in the treatment of osteoarthritis in dogs, despite unfavorable pharmacological findings and a lack of supportive clinical data.4

Two major metabolites of tramadol, O-desmethytramadol and N,O-didesmethyltramadol, are credited with its pharmacological effects.3 Studies3,4 have shown that the μ-opioid receptor effects (ie, centrally acting analgesia due to μ-opioid receptor agonism) are primarily attributable to O-desmethytramadol, yet in dogs, very little of this metabolite is produced during the metabolism of tramadol. Furthermore, data regarding repetitive tramadol administration to dogs indicate that plasma O-desmethytramadol concentrations decrease by 60% to 70% within just 1 week.3 Still, because of crowdsourced websites and continuing education lectures purporting the safety of tramadol for dogs and the limited availability of pharmacokinetic data, the veterinary community continues to support the use of tramadol across a wide range of doses, spanning from 1 to 10 mg/kg (0.45 to 4.5 mg/lb).3–5

In a randomized clinical trial3 involving a small group of dogs with osteoarthritis, limited improvements were detected in subjective outcome measurements when dogs were treated with tramadol; however, no improvement in objective outcome measurements...
was demonstrated. Therefore, given the paucity of available clinical data, the purpose of the study reported here was to investigate through a blinded, randomized clinical trial the effectiveness of tramadol for treatment of osteoarthritis in dogs. Our primary hypothesis was that changes from baseline in clinical signs of osteoarthritis-associated pain and orthopedic dysfunction, as measured via vertical GRF data and CBPI scores, would not differ significantly between tramadol and placebo treatment. The second hypothesis was that changes in GRF data and the proportion of dogs with a CBPI-defined positive treatment response would be greater with carprofen treatment versus placebo treatment.

Materials and Methods

Animals

Client-owned dogs of any breed, age, or sex, weighing 15 to 50 kg (33 to 110 lb) and with osteoarthritis-associated signs of pain and dysfunction in the elbow or stifle joint, were recruited for the study from January 2015 to May 2017. All dog owners received a detailed description of the protocol and were required to provide signed consent before their dog was evaluated for inclusion in the study. The Clinical Research Committee of the College of Veterinary Medicine, University of Georgia, approved the study protocol.

Owners of included dogs were required to maintain a stable daily activity routine for their dog throughout the study period. Dogs were excluded if they received corticosteroid medications or injectable polysulfated glycosaminoglycans orally or parenterally ≤30 days before or during the study. No additional analgesics such as NSAIDs were allowed while participating, and an initial washout period of at least 7 days was required for any analgesics administered before any pretreatment (baseline) measurements were made.

Patient screening at baseline included a physical examination, CBC, serum biochemical analysis, and urinalysis. Radiographs were acquired of all appendicular joints for which signs of pain were apparent. Documentation of osteoarthritis in at least 1 elbow or stifle joint was required for inclusion; if the osteoarthritis was bilateral (ie, in both elbow or both stifle joints) or affected both an elbow and stifle joint, the most clinically affected joint was designated as the joint of interest. Additional exclusion criteria included suspected or demonstrated systemic or local disease other than osteoarthritis, evidence of instability in any joint (eg, cranial cruciate ligament damage), joint surgery within the last 12 months, or clinical osteoarthritis in other joints in addition to the elbow or stifle joint.

An a priori sample size calculation was performed with the intention of providing 80% power to detect a difference among treatments (in a crossover study design) on the basis of data from prior clinical trials regarding GRFs (PVF and VI) and CBPI scores. For VI, a change of 1.0 (percentage change in body weight per second) was deemed a clinically meaningful change, and the desired sample size for this variable was 18 (SD, 0.3; α = 0.05). For CBPI score, a percentage difference of 30% between treatments was used, yielding a sample size of 35 (SD, 40%; α = 0.05). An attempt was consequently made to enroll at least 35 dogs.

Study protocol

A randomized, blinded, placebo- and positive-controlled crossover study design was used in which dogs were assigned to receive each of 3 treatments in random order. This random order was assigned a priori by use of a computer program that generated a simple randomized drug-dispensing schedule. The pharmacy then dispensed the following products in opaque, identically appearing capsules in amounts tailored to each dog’s body weight at the beginning of the treatment period that allowed for each product to be administered 3 times/d (morning, midday, and night) with both owners and investigators blinded to treatment identity: placebo (lactose powder; negative control treatment); carprofen at 2.2 mg/kg (1 mg/lb), every 12 hours (morning and night), with a placebo capsule for the midday dose (positive control treatment); or tramadol hydrochloride at 5 mg/kg (2.3 mg/lb), every 8 hours (treatment of interest). Prior to each treatment session, owners were provided with 3 identically appearing medication vials labeled morning, midday, and evening that contained the assigned treatment for the particular session and told to administer the capsules orally for 10 days.

Dogs were withdrawn from the study, prior to study completion, if they appeared intolerant of the medication, owners believed the degree of provided pain control was unacceptable, or dogs developed a condition that would have excluded them from enrollment at the start. Throughout the study, owners were supplied with codeine-acetaminophen (1 to 2 mg of codeine/kg [0.45 to 0.91 mg of codeine/lb]) as a rescue medication with instructions to administer this medication to their dog every 8 hours if they believed their dog had unacceptable signs of pain. This particular drug was chosen because it was not an NSAID and its actions were short-lived and therefore would not interfere with subsequent treatment periods. Owners recorded any provision of rescue medication on a form provided to them.

Outcome measurements

The primary outcome of interest was percent change from baseline in VI measurements over each treatment period. Secondary outcomes included change from baseline in PVF measurements and proportion of dogs with a CBPI-defined positive treatment response. Accordingly, vertical GRF data (VI and PVF) were collected for all 4 limbs by means of 2 in-series force platforms and with the aid of a dedicated computer and software program. Gaits of each dog were assessed by the same investigator (SCB...
and BTT (both board-certified veterinary surgeons) before each treatment period began (baseline) and again on the final day of each treatment period (day 10). For all measurements, dogs were encouraged to trot over the force platforms at a velocity of 1.7 to 2.1 m/s and acceleration of -0.5 to 0.5 m/s². Data from 5 valid trials were collected for analysis. For comparisons, VI and PVF values were subsequently normalized as a percentage of body weight for each dog.

Treatment response assessments (positive responder or nonresponder) were determined by assignment of CBPI scores (by the client) before and at the end of each treatment period. Briefly, the CBPI system involves assignment of scores ranging from 0 to 10 on the basis of the degree to which pain appears to interfere with 6 daily activities (PIS; 0 = no interference and 10 = complete interference) and perceived pain severity (PPS; 0 = no pain and 10 = severe pain). For study purposes, a positive response was defined as a score decrease between baseline and day 10 of ≥1 for PSS and ≥2 for PIS.

Statistical analysis
Blinding to treatment identity was broken when the last dog completed the final treatment period and prior to any analyses of the data. Dog age and body weight were summarized as mean ± SD. Vertical GRF data (VI and PVF) were compared among and within treatments by means of repeated-measured ANOVA, with the Tukey test performed to adjust for multiple comparisons. Proportions of dogs with a positive response to treatment as defined by changes from baseline in CBPI scores were compared among treatments by means of the χ² test. Proportions of dogs requiring rescue medication were also compared among treatments by means of the χ² test. All tests were 2 sided, and values of P < 0.05 were considered significant. All analyses were performed with statistical software.

Results
Animals
Forty dogs were enrolled in the study; however, 5 dogs did not complete the study or were withdrawn. These 5 dogs included 1 that developed a contralateral cruciate ligament injury, 1 that received corticosteroid treatment for allergies, 1 that had a traumatic injury, and 2 that were withdrawn by their owners for unspecified reasons. All 5 were excluded from the statistical analysis, leaving 35 dogs in the study.

Eleven of the 35 (31%) included dogs had osteoarthritis of the elbow joint. Mean ± SD age of this group was 8.5 ± 3.9 years, and mean body weight was 31.2 ± 9.5 kg (68.6 ± 20.9 lb). Twenty-four (69%) included dogs had osteoarthritis of the stifle joint. Mean age of this group was 8.4 ± 4.0 years, and mean body weight was 31.3 ± 7.8 kg (68.9 ± 17.2 lb).

Rescue medication was administered by the owners of 4 dogs (3 during the placebo session and 1 during the carprofen session). No significant difference in proportions of dogs receiving rescue medication was identified among treatments. Statistical analysis revealed no time-by-treatment interactions during the study, indicating that the randomly assigned order in which the treatments were given had no influence on treatment outcomes.

VI and PVF
With placebo and tramadol treatment, no significant differences in VI and PVF were identified between baseline (pretreatment) and day 10 measurements (Figures 1 and 2). However, with carprofen treatment, both VI and PVF increased significantly.
from baseline values. Additionally, the change from baseline in VI and PVF values was significantly greater with carprofen treatment than with placebo or tramadol treatment.

**CBPI scores**

Only 33 (94%) dogs were included in statistical analyses of CBPI data owing to incomplete data for 2 dogs. The proportion of dogs deemed to have a positive response (ie, decrease in PSS of \( \geq 1 \) and in PIS of \( \geq 2 \)) with carprofen treatment (14/33 [42%]) by means of this scoring system was significantly greater than with tramadol (8/33 [24%]; \( P = 0.01 \)) or placebo (7/33 [21%]; \( P = 0.001 \)) treatment. No significant difference in this variable was identified between placebo and tramadol treatment.

**Discussion**

Findings of the present study supported our hypothesis that tramadol (5 mg/kg, PO, q 8 h) would be no more effective than placebo in the treatment of pain and orthopedic dysfunction in dogs with osteoarthritis of the elbow or stifle joint. Data regarding the primary outcome variable (VI) yielded no evidence of improvement following tramadol treatment, compared with baseline or placebo data. Additionally, data regarding both secondary outcome variables (PVF and CBPI classification) suggested no improvement with tramadol treatment, compared with baseline or placebo data. These data were in stark contrast with common recommendations for the use of tramadol to treat osteoarthritic-associated pain in dogs.\(^ {13,14} \) The present study represented the first specifically designed, randomized, placebo-controlled clinical trial of tramadol as sole treatment for osteoarthritis-associated pain in dogs. The source of the data used to support tramadol administration for this purpose in previous publications is unclear.

The outcome variables measured in the present study have been widely accepted and established for research of this manner and have known variance. This strengthened our confidence that the results were valid and clinically important. However, even with well-established metrics such as these, differences among studies in definitions of treatment response can affect the results. For example, the CBPI data obtained in the present study contradicted those in a previous study,\(^ 3 \) in which an improvement in overall CBPI score was identified for dogs with osteoarthritis receiving tramadol as sole treatment. The most likely reason for this disparity is the method of CBPI data evaluation and the definition of treatment response in each study. In the previous study,\(^ 3 \) absolute change in overall CBPI score was used as the outcome measurement; however, in the present study, a positive treatment response was defined as a score reduction \( \geq 1 \) for PSS and \( \geq 2 \) for PIS as recommended by Brown et al.\(^ 8 \) Interestingly, in the previous study,\(^ 3 \) overall CBPI score was the only outcome variable measured to evaluate response to tramadol administration. That study also involved dogs with clinical signs of osteoarthritis in the hip joint rather than elbow or stifle joint, although ranges in age and body weight of dogs were similar between studies. Differences in outcomes between studies may have been attributable to the joints assessed; however, such variation has yet to be documented in the veterinary literature. Furthermore, both studies involved enrollment of patients at academic sites, so the study populations may have been more homogeneous than the general population of pet dogs with osteoarthritis.

The second hypothesis of the present study was also supported, given that carprofen treatment resulted in significant differences from placebo treatment for all 3 outcome variables. The different responses to the negative (placebo) and positive (carprofen) control treatments were as expected, strengthening conclusions regarding tramadol treatment. With placebo treatment, dogs had no improvement in vertical GRF values (VI and PVF). This was consistent with previously reported findings.\(^ {6,10,15,16} \) Additionally, CBPI data suggested an improvement in only 21% of dogs with placebo treatment, which is lower than the 38% reported previously.\(^ 8 \) However, when dogs received carprofen, an improvement was observed in vertical GRF data as well as CBPI scores, which is consistent with previously reported kinetic data\(^ {6,15–17} \) and CBPI data\(^ 6,8 \) for osteoarthritic dogs treated with NSAIDs. Therefore, the negative and positive control treatment periods of the present study yielded repeatable and expected results to bolster the conclusion that treatment with tramadol had no beneficial effects on signs of pain and orthopedic dysfunction of dogs with osteoarthritis of the elbow or stifle joint. This lack of beneficial effect was not surprising given the pharmacokinetic and pharmacodynamic data available for dogs regarding tramadol.\(^ 3–5 \) Tramadol has a brief half-life in dogs, and serum tramadol concentration decreases with repeated use.\(^ 3–5 \) Additionally, data suggest that tramadol has limited to no effect on acute thermal and mechanical cutaneous nociception in dogs.\(^ 18 \)

The present study involved a crossover design, in which each dog served as its own control subject. This study design has several advantages over a parallel dose design, in which the comparison group or groups comprise subjects other than those receiving the treatment of interest. Problems typically encountered during comparisons of groups comprising different subjects, such as any confounding effects of subject age and sex, are avoided. Fewer subjects are required in a crossover design than in a parallel design to attain the same degree of statistical power and identify a treatment effect. In the study reported here, a priori calculations indicated that a sample size of 35 dogs would be required to achieve a statistical power of 80% at the specified effect size. However, if a similar study were undertaken involving a parallel design, nearly 130 dogs would be needed per group to achieve the same statistical power, representing a 271% increase in the number of dogs required.
A potential limitation to the crossover study design is the carryover effect, by which the effects of 1 treatment extend into the next treatment period, assuming the subsequent treatment had effects that were actually attributable to the previous treatment period. However, the carprofen and tramadol products used in the present study have short half-lives in dogs, their effects are reversible, and in the management of osteoarthritis the products are considered to treat the signs of osteoarthritis and not the underlying pathological condition. Additionally, a washout period was provided and new baseline data were collected before each treatment period began to minimize any carryover effects that might have affected the data. The finding of no time-by-treatment interaction on statistical analysis further strengthened our confidence that no carryover effects biased the results.

Another potential weakness of the crossover design would be if some subjects dropped out after 1 treatment, without receiving the other treatment or treatments, particularly if the reason for dropping out was adverse treatment effects. However, no dog dropped out or was withdrawn from the present study because of adverse effects. Use of >1 study site in different geographic locations could be considered advantageous to provide a more heterogeneous and representative population with broader generalizability, particularly if the measured outcome variable involves subjective owner evaluations.

Another possible limitation of the present study was that the sample size calculations had been based on data from studies involving NSAIDS but not tramadol, so the possibility of type II error could not be ruled out. However, the similarity in treatment effect between tramadol and placebo suggested that an enormous sample size would have been needed to identify a statistical difference that may not have been clinically meaningful.

The promotion and proliferation of tramadol administration for dogs with osteoarthritis over the past 10 to 15 years are a curious phenomenon. Belief in the efficacy of tramadol may in part be due to the so-called caregiver placebo effect, which has been well documented in the management of diseases in dogs, including osteoarthritis. Clinician bias stemming from prior treatment success with a few patients may also play a role. For example, in the present study, a small number of dogs had improvements in all outcome variables with tramadol treatment. Widespread use of tramadol despite a lack of scientific evidence to support any beneficial effects may have evolved from the limited experiences of some clinicians that were then unwittingly promoted (without proper scientific validation) in non-peer-reviewed venues such as continuing education presentations, professional discussion websites, crowdsourced websites, social media, and review articles. This use of tramadol is a classic example of failing to acknowledge and control for bias when evaluating a potential treatment. Variations within and among patients are observed daily by clinicians. Therefore, it is imperative to differentiate the expected variations in patient responses from the effects attributable to an intervention, such as with the use of tramadol for managing osteoarthritis-associated pain and orthopedic dysfunction in dogs. Data from the present study provided no support for the use of tramadol in dogs with osteoarthritis of the elbow and stifle joint. We believe it highly likely that our findings can be generalized to other joints in dogs with osteoarthritis as well.

Acknowledgments

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Footnotes

b. Colored gelatin empty capsule (size 0 or 00), Capsuline, Pompano Beach, Fla.
e. Sun Pharmaceutical Industries, Cranbury, NJ.
f. Mallinckrodt Inc, Hazelwood, Mo.
g. Model OR-6-6, Advanced Mechanical Technology Inc, Newton, Mass.

References

11. Stejskal M, Torres BT, Sandberg GS, et al. Variability of ver-


From this month’s AJVR

Magnetic resonance imaging evaluation of olfactory bulb angle and soft palate dimensions in brachycephalic and nonbrachycephalic dogs

David A. Barker et al

OBJECTIVE
To determine from MRI measurements whether soft palate length (SPL) and thickness are correlated, evaluate the association between the olfactory bulb angle (OBA) and degree of brachycephalia, and determine the correlation between soft palate–epiglottis overlap and OBA in dogs.

ANIMALS
50 brachycephalic and 50 nonbrachycephalic client-owned dogs without abnormalities of the head.

PROCEDURES
Medical records and archived midsagittal T2-weighted MRI images of brachycephalic and nonbrachycephalic dogs’ heads were reviewed. Group assignment was based on breed. Data collected included weight, SPL and thickness, OBA, and the distance between the caudal extremity of the soft palate and the basihyoid. Soft palate length and thickness were adjusted on the basis of body weight.

RESULTS
Brachycephalic dogs had significantly thicker soft palates and lower OBAs, compared with findings for nonbrachycephalic dogs. There was a significant negative correlation ($r^2 = 0.45$) between OBA and soft palate thickness. The correlation between SPL and OBA was less profound ($r^2 = 0.09$). The distance between the caudal extremity of the soft palate and the basihyoid was shorter in brachycephalic dogs than in nonbrachycephalic dogs. The percentage of epiglottis–soft palate overlap significantly decreased with increasing OBA ($r^2 = 0.31$).

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that MRI images can be consistently used to assess anatomic landmarks for measurement of SPL and thickness, OBA, and soft palate-to-epiglottis distance in brachycephalic and nonbrachycephalic dogs. The percentage of epiglottis–soft palate overlap was significantly greater in brachycephalic dogs and was correlated to the degree of brachycephalia. (Am J Vet Res 2018;79:170–176)