Use of trazodone to facilitate postsurgical confinement in dogs

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Objective—To investigate the safety and efficacy of oral administration of the serotonin antagonist and reuptake inhibitor trazodone hydrochloride to facilitate confinement and calming after orthopedic surgery in dogs.

Design—Prospective open-label clinical trial.

Animals—36 client-owned dogs that underwent orthopedic surgery.

Procedures—Starting the day after surgery, dogs were administered trazodone (approx 3.5 mg/kg [1.6 mg/lb], PO, q 12 h) with tramadol (4 to 6 mg/kg [1.8 to 2.7 mg/lb], PO, q 8 to 12 h) for pain management. After 3 days, administration of tramadol was discontinued, and the trazodone dosage was increased (approx 7 mg/kg [3.2 mg/lb], PO, q 12 h) and maintained for at least 4 weeks. If needed, trazodone dosage was increased (7 to 10 mg/kg [3.2 to 4.5 mg/lb], PO, q 8 h). Owners completed electronic surveys rating their dogs’ confinement tolerance, calmness or hyperactivity level, and responses to specific provocative situations prior to surgery and 1, 2, 3, and 4 weeks after surgery and at the postsurgery evaluation (at 8 to 12 weeks).

Results—Most (32/36 [89%]) of owners reported that their dogs, when given trazodone during the 8 to 12 weeks following orthopedic surgery, improved moderately or extremely with regard to confinement tolerance and calmness. Trazodone was well tolerated, even in combination with NSAIDs, antimicrobials, and other medications; no dogs were withdrawn from the study because of adverse reactions. Owner-reported median onset of action of trazodone was 31 to 45 minutes, and median duration of action was ≥4 hours.

Conclusions and Clinical Relevance—Results suggested that oral administration of trazodone was safe and efficacious and may be used to facilitate confinement and enhance behavioral calmness of dogs during the critical recovery period following orthopedic surgery. (J Am Vet Med Assoc 2014;245:296–301)

For optimal treatment success of elective orthopedic surgeries in dogs, such as stifle joint stabilization following cranial cruciate ligament tear, effective postsurgical management is critical. Typical management includes a 6- to 12-week postsurgical period of confinement and exercise restriction. Because dogs may be young,1 active, healthy, and unaccustomed to confinement, implementation of postsurgical instructions is often challenging to owners. Failure to comply with activity restriction may lead to protracted recovery or even surgical treatment failure, necessitating a second surgical procedure.2

Historically, the phenothiazine tranquilizer acepromazine maleate3 has been used to facilitate confinement, but this agent may cause excessive sedation1 and increase the risk of falling. Acepromazine may also cause paradoxical excitation and a range of physiologic effects.3 There is a need for a well-tolerated orally administered agent to facilitate confinement after orthopedic surgery without causing adverse effects.

The atypical antidepressant trazodone hydrochloride4 is a medication with a long track record of safe use in humans for the treatment of anxiety and depression and to facilitate sleep, particularly in combination with selective serotonin reuptake inhibitors.3 Trazodone is classified as a serotonin (5-hydroxytryptamine) antagonist and reuptake inhibitor, with complex effects on serotonergic systems. In humans, trazodone, at low to moderate dosages, acts to antagonize postsynaptic 5-hydroxytryptamine2A receptors, as well as histaminic and α1 adrenergic receptors, which may account for its moderate hypnotic effects.6 At higher dosages, trazodone also acts as an antagonist at postsynaptic 5-hydroxytryptamine2C receptors.6 Its active metabolite, m-chlorophenylpiperazine, is a potent direct 5-hydroxytryptamine2C receptor agonist. Trazodone has minimal effects on muscarinic cholinergic receptors and so has few anticholinergic adverse effects. In mammals tested, trazodone has a wide safe dosage range. The oral LD50 of trazodone is high: 610 mg/kg (221 mg/lb) in rats, and 560 mg/kg (255 mg/lb) in rabbits.7 The LD50 in dogs has not been determined.
In humans, trazodone is generally well tolerated at an oral dosage range from 150 to 600 mg/d,8 alone and in combination with other drugs (excepting monoamine oxidase inhibitors for which concurrent use is contraindicated). Trazodone is commonly prescribed as a sleep aid for patients prescribed antidepressants in the selective serotonin reuptake inhibitor class. Trazodone has minimal if any effect on seizure threshold.9 In its generic formulation, trazodone is widely prescribed. On the basis of prescription frequency, trazodone HCl was ranked 29th among the top 200 prescription drugs for 2010,10 with > 18 million prescriptions written for its use by physicians in the United States. The long history of safe use in humans, alone and in combination with other medications, suggests that trazodone may be a useful therapeutic agent in dogs.

In dogs, trazodone has been used in the treatment of anxiety disorders, alone or in combination with other behavioral medications.11,12 The drug-enhanced behavioral calmness and reduced anxiety improve patient welfare with few adverse effects. A recent single-dose pharmacokinetic study13 of trazodone in 6 dogs found that when given orally, trazodone induced mild sedation with no observable adverse effects. In anesthetized dogs, trazodone has little effect on cardiac function, compared with equally effective dosages of imipramine.14 These characteristics make trazodone an ideal agent to decrease anxiety, agitation, and distress associated with confinement in dogs after surgery.

In a pilot study,15 17 dogs were administered trazodone (3.5 to 7 mg/kg [1.6 to 3.2 mg/lb], q 12 h, for ≥ 4 weeks) following orthopedic surgery. A dosage increase (to approx 8 to 10 mg/kg [3.6 to 4.5 mg/lb], q 12 h) was permitted. No adverse effects were reported, and owners reported that the drug was effective. Therefore, the purpose of the study reported here was to investigate the safety and efficacy of oral administration of trazodone hydrochloride to facilitate confinement and calming after orthopedic surgery in dogs in a larger clinical trial. The hypothesis was that, per owners’ assessment of their dogs’ behavior, the use of trazodone would be safe and facilitate confinement and enhance behavioral calmness following orthopedic surgery in dogs.

Materials and Methods

All procedures were approved by the North Carolina State University Institutional Animal Care and Use Committee before commencement of the study, and informed consent was obtained from owners of all enrolled dogs. Dogs admitted to the North Carolina State University College of Veterinary Medicine Veterinary Health Complex for orthopedic surgery were recruited into this study. Dogs were eligible for enrollment if they were in good health, weighed at least 5 kg (11 lb), and were not receiving concomitant behavioral medications or monoamine oxidase inhibitors, such as amitraz products. Because of the rare adverse effect of priapism (retained penile erection) associated with trazodone use in humans15 and to avoid any potential reproductive consequences, only castrated males and spayed females were enrolled. Prior to surgery, dogs were evaluated for general health by physical examination and routine laboratory assessment.

Owners were eligible to enroll their dogs if they agreed to administer medication as directed, report any adverse effects, and be responsible for completing a weekly online survey regarding features of their dog’s behavior critical to postorthopedic surgical management. In homes with multiple caregivers, 1 owner was designated to complete the weekly surveys. All participating owners signed an informed consent form and were provided with emergency contact information. At the time of enrollment, owners were asked by the study technician to complete a presurgical survey that evaluated their dogs’ behavior in response to 5 provocative situations, relevant to successful postorthopedic surgical management, and 1 temperament measure. The survey asked owners to rate their dogs’ tolerance of confinement when left alone, tolerance of confinement when the owner was at home, tendency to pull on a leash during walks, willingness to be controlled by the owner (ie, obey familiar commands), intensity of greeting behavior to the owner and other familiar persons, and overall calmness. Lower scores reflected calmer, more manageable dogs.

After surgery, all owners were provided written emergency contact information and standardized instructions for postsurgical confinement and activity restriction for the following 4 to 12 weeks (depending on the specific surgery). Details of confinement varied from dog to dog, but generally consisted of a crate, small pen, or small room. Dogs were prescribed trazodone on the basis of body weight, to be given twice daily PO for at least 4 weeks. For the first 3 postsurgical days, owners were instructed to administer trazodone at an initiation dosage (half the standard dosage, approximately 3.5 mg/kg, PO, q 12 h) as well as the analgesic tramadol4 (4 to 6 mg/kg [1.8 to 2.7 mg/lb], PO, q 8 to 12 h), a drug with serotoninergic activity.16 The low initiation dosage of trazodone was chosen to establish initial blood concentrations, develop tolerance to transient sedating effects of trazodone, and avoid the possibility of serotonin excess.17 After 3 days, tramadol administration was discontinued, and trazodone dosage was increased to the standard dosage (approx 7 mg/kg, PO, q 12 h). If, during the study, the standard dosage was considered by the owner to be insufficient, after consultation with a veterinary behaviorist, the dosage and administration schedule of trazodone were increased (approx 7 to 10 mg/kg, PO, q 8 h). For useful comparisons between the standard and high dosages, total daily dose was calculated as the total amount of trazodone administered PO during a 24-hour period.

Depending on the surgeon’s prescription during the postsurgical period, any dog could receive other concomitant drugs PO or topically for a variable number of days to weeks including NSAIIDs, buprenorphine, amantadine, or antimicrobials. During the course of the study, dogs continued to receive routine heartworm and flea prophylaxis as directed by their primary veterinarian.

Data collection—Each week for 4 weeks following surgery, owners were sent, via email, a link to an online survey to evaluate their dog’s postsurgical behavior. A final fifth survey was completed at the time of the final patient evaluation, 8 to 12 weeks after surgery. The surveys for postsurgical weeks 1, 2, 3, and 4 and the final
survey repeated questions on the presurgery survey. In addition, owners were asked to assess the usefulness of trazodone administration with regard to confinement tolerance and calming on a 4-point ordinal scale from not at all helpful to extremely helpful. A low score was associated with greater confinement tolerance and calming.

On each survey, owners were asked to confirm the dosage and schedule of trazodone administered and the latency and duration of effect as well as list any concomitant medications that were given. Owners were queried about adverse events in each survey in a free-text field and were encouraged to contact study personnel at any point if they had questions or believed that the dog’s trazodone dosage was inadequate. After 4 weeks of medication administration, the study technician called each owner by telephone to discuss the option to continue trazodone administration until the final 8- to 12-week postsurgical visit. At the final postsurgical visit, laboratory tests (CBC and serum biochemical profile) were collected for comparison with the presurgical laboratory values. As an incentive for completion of the surveys, costs of the trazodone and the postsurgical laboratory tests were covered by the study.

Withdrawal from study—Owners were permitted to withdraw their dog from the study at any time and for any reason. Surgeons and investigators could withdraw dogs from the study if they were concerned about the health or comfort of the dog. Investigators could also withdraw dogs if owners were noncompliant with the administration and reporting requirements of the study.

Statistical analysis—Data obtained from owner rating scales were analyzed by means of nonparametric statistics. The Cochran-Mantel-Haenszel test was used for analysis of ordinal data. Results from the final survey for each dog were used to evaluate overall response. Improvement was defined as change from baseline in a positive direction. The group of dogs that received trazodone 3 times daily (high dosage) was compared with dogs that received trazodone twice daily (standard dosage) to determine whether there were differences in age, weight, or baseline ratings that might have identified these dogs a priori. Dogs were also classified by surgery type (hip joint, stifle joint, or other), and groups were analyzed for differences in age, weight, and total dose and schedule of trazodone. For all tests, values of \( P < 0.05 \) were considered significant. Descriptive statistics are expressed as mean ± SD.

Results

Forty-one dogs were enrolled in this trial (22 castrated males and 19 spayed females). Thirty-six dogs completed the trial. Four dogs were withdrawn because of owner noncompliance with online surveys and communications; 1 dog was withdrawn when it was determined it was concurrently receiving fluoxetine. No owners elected withdrawal, and no dogs were withdrawn for adverse events. For the 36 dogs that completed the trial, 52.2% were female, the mean age was 3.0 ± 2.46 years, and the mean weight was 32.0 ± 10.6 kg (70.4 ± 23.3 lb).

Surgeries—The 36 dogs in the study underwent a variety of elective orthopedic surgeries, including stabilization of a medially luxated patella (n = 3), triple tibial tuberosity osteotomy for cranial cruciate ligament tear (17), tibial wedge osteotomy for cranial cruciate ligament tear (1), total hip replacement (11), external fixator placement for fracture repair (3), and removal of a fragmented medial coronoid process (1). These were further grouped by surgery type, and the distribution of dogs was hip joint (n = 11), stifle joint (21), and other (4). No significant group differences were found between the hip (n = 21) and stifle (11) joint groups for age (\( P = 0.143 \)) or weight (\( P = 0.365 \)). Because of the small number of dogs in the other category and the diversity of surgeries in that group, these dogs were excluded from the analysis of group differences by surgery type.

Trazodone dosage and schedule—After the postsurgical initiation dosage, the mean standard daily dosage at week 2 was 13.73 mg/kg (6.24 mg/lb), divided into twice-daily doses (mean, 6.86 mg/kg [3.12 mg/lb], q 12 h). At various times after week 2, 11 (29.7%) owners requested an increase in the dosage of trazodone for their dogs to improve confinement tolerance, and these dogs became the high-dosage group. Considering that increases in dosage may have taken place during different weeks after week 2, the highest daily dosage each dog received during the study period was defined as the peak dosage. When increased, the mean peak dosage for the 11 dogs was 7.06 mg/kg (3.21 mg/lb), PO, every 8 hours. Mean total daily peak dosage was 21.19 ± 6.39 mg/kg (9.63 ± 2.90 mg/lb), PO. The dogs in the high-dosage group (n = 25) did not differ significantly from those that received the standard dosage (n = 11) on the basis of age (\( P = 0.568 \)) or weight (\( P = 0.770 \)). When analyzed by surgery type (hip [n = 11] vs stifle [21]), there was no significant (\( P = 0.922 \)) difference for peak daily dosage given. There was also no significant (\( P = 0.703 \)) difference in the distribution of dogs in the high dosage group versus the standard dosage group by surgery type.

Trazodone onset of action and duration—As reported by owners on the final survey, the median latency to trazodone effect was 31 to 45 minutes after administration. More than 90% of owners reported latency of effect between 16 and 90 minutes after administration. The median duration of action was reported to be ≥ 4 hours.

Behavioral outcomes—The final survey responses, compared with the presurgical survey responses, revealed that dogs treated with trazodone significantly improved with respect to the intensity of greeting behavior to the owner and to other familiar persons (\( P = 0.003 \)) and with respect to overall calmness (\( P = 0.032 \)). Dogs treated with trazodone did not significantly improve with respect to willingness to be controlled by the owner (ie, obey familiar commands; \( P = 0.492 \)) and tendency to pull on a leash during walks (\( P = 0.097 \)). Dogs that received the standard dosage versus a high dosage of trazodone did not differ in their presurgical rating of calmness (\( P = 0.670 \)) or in measures of confinement tolerance (\( P = 0.470 \)).
Effect of trazodone on confinement tolerance and calming—In the final survey, 89% (32/36) of all owners rated trazodone as moderately or extremely helpful for confinement tolerance. In contrast, at week 1, before attaining a full week at the standard dosage, trazodone was evaluated as moderately or extremely helpful for confinement tolerance by 58% (21/36) of all owners. No owners rated trazodone as not at all helpful in facilitating confinement tolerance. At the final survey, trazodone was more likely to be reported as extremely helpful in dogs that initially resisted confinement, compared with those that initially accepted confinement (P = 0.011).

In the final survey, 89% (32/36) of all owners rated trazodone as moderately or extremely helpful for calming. In contrast, at week 1, trazodone was evaluated as moderately or extremely helpful for calming by 61% (22/36) of owners. At study completion, 25 of 36 (69.4%) dogs continued to receive trazodone in accordance with the owner’s request. Of these 25, 4 (16%) dogs received trazodone once daily, 16 (64%) dogs received trazodone twice daily, and 5 (20%) dogs received trazodone 3 times daily.

Adverse events—Owners were queried about adverse events in each weekly survey and were able to respond in a free-text field. Over the course of the study, ≥1 adverse event that occurred ≥1 time was recorded for 20 (55.5%) dogs (Table 1). No dog was withdrawn from the study because of an adverse event. No owners reported seizures, ongoing akathisia (state of motor restlessness), or priapism. No dogs had signs consistent with serotonin syndrome. Two incidents resulted in dogs accidentally receiving higher dosages of trazodone than prescribed. One male dog was accidentally given 2 doses, receiving a total trazodone dose of 600 mg (20 mg/kg [9 mg/lb], PO). The dog was evaluated by the Emergency Service and assessed as slightly sleepy with no abnormal results of physical examination or blood analyses; the dog recovered at home without complications. In another case, an owner erroneously continued tramadol administration for >3 days, such that therapeutic dosages of tramadol and the standard dosage (rather than initiation dosage) of trazodone were administered concurrently for 2 weeks; no adverse events were reported.

Concomitant medications—During the study, dogs were administered concomitant medications as prescribed by their orthopedic surgeon or primary veterinarian. These medications, recorded by each owner on the weekly survey, covered a wide range of medication classes (Table 2) and were administered at various doses and durations. No adverse events were reported by owners in response to concomitant medication administration.

Laboratory values—Serum biochemical and CBC values before surgery and at the final visit (0 to 4 weeks after administration of trazodone was completed) were independently evaluated by surgical clinicians and residents. The few values not within laboratory reference ranges were not considered clinically important.

Discussion

In terms of efficacy, approximately 90% of owners reported moderate or extremely positive effects of their dogs’ treatment with trazodone to facilitate postsurgical confinement tolerance and calming. Compared with presurgical baseline behavioral assessments, intensity of owner-
er greeting and overall calmness improved over the course of the study. There was no positive or negative effect of trazodone on the tendency of dogs to pull on a leash during walks and willingness to be controlled by the owner (i.e., obey familiar commands), suggesting that administration of trazodone did not improve or inhibit trained responses.

In terms of safety, trazodone was well tolerated at any dosage administered. There were no veterinary recommendations to discontinue trazodone administration during the study, and no owner discontinued use of trazodone. During the study, there were no adverse effects that required medical treatment, dosage adjustment, or withdrawal of trazodone. The most common adverse effect in dogs that received trazodone was a transient state of somnolence, but no owners reported ataxia, disorientation, or stumbling. Thus, there appeared to be no motor impairment that might contribute to a fall during the surgery recovery phase. Other adverse effects were uncommon and manageable. One dog was accidentally given trazodone at a dose of 20 mg/kg but had no adverse events per veterinary evaluation except sleepiness. Priapism, a rare adverse effect associated with trazodone use in human males, was not observed in any dog at any dosage. Transient anxiety, restlessness, or agitation was reported by 2 owners as a single adverse event. Because of its short duration, the reported behavior was not consistent with akathisia, an ongoing state of motor restlessness. Akathisia is a potential adverse effect of behavioral drugs but not commonly reported as a consequence of the use of trazodone in humans. In fact, trazodone has been reported to be therapeutic for the treatment of neuroleptic-induced akathisia.18

At the conclusion of the study, all dogs were physically examined by veterinary surgeons or surgical residents, and no clinical abnormalities were observed. Although evaluation of poststudy laboratory results revealed values outside the laboratory reference range for some dogs, these were considered by clinicians to not be clinically important. None required further evaluation. During the study, trazodone was safely administered with a range of concomitant medications, including NSAIDs and antimicrobials, as disclosed by owners on each survey. In general, NSAIDs were administered for up to 7 days following surgery. Owing to the ability of NSAIDs to decrease signs of pain and therefore influence pain-related behavior, this was a potential confounding factor in the study.

Because of concerns that concurrent use of 2 serotonergic agents, tramadol and trazodone, might result in an excess of serotonin, trazodone was administered at a subtherapeutic initiation half-dosage until tramadol use was discontinued. Tramadol, a centrally acting synthetic analgesic, is in the opioid class of drugs. Its action may inhibit the reuptake of serotonin,19 potentially leading to a toxic concentration of serotonin in the CNS, a condition called serotonin syndrome. Signs of serotonin syndrome may include neurologic signs of disorientation or confusion, motor restlessness, hyperreflexia, myoclonus, tremor, seizures, gastrointestinal tract signs including vomiting and diarrhea, and signs of physiologic decompensation such as hyperthermia.16,20

In the present study, no dogs had any signs consistent with serotonin syndrome. One owner, in error, administered the standard dosage of trazodone in combination with tramadol for 1 week without negative effect. Most owners reported that trazodone acted promptly, with the median onset of action of oral administration within 31 to 45 minutes. By owner report, the duration of action of trazodone was ≥4 hours. In humans, orally administered trazodone undergoes a biphasic elimination pattern with a fast phase of 3 to 5 hours followed by a slower phase lasting 6 to 9 hours.8 A pharmacokinetic study13 of a single orally administered dose of trazodone in dogs revealed an elimination half-life of (mean ± SD) 166 ± 47 minutes. In the present study, in dogs in which the duration of action seemed insufficient, the trazodone administration schedule was increased to 3 times daily.

Peak daily dosages administered to dogs in the present study ranged from 8.0 to 30.9 mg/kg (14.0 mg/lb/d); all dosages were divided into 2 or 3 doses/d. Dogs, similar to humans, appear to have a wide effective and safe dosage range of trazodone.

In general, owners were gratified by the positive effect of trazodone on their dogs and commented favorably in the free-text portion of the survey on the effectiveness of trazodone as an aid to necessary postsurgical confinement. Despite the necessity of administering medication orally to their dogs daily, the majority (69%) of owners chose to continue use of trazodone after the first 4 weeks. The open trial did not allow evaluation of the placebo effect known to be present in human and veterinary studies.21,22,23 Positive findings could have been due to a conditioned (learned) response of the dog to confinement over time, response to behavioral correction administered by the owner, or positive owner expectations following specialty surgery. It is also possible that owners could have misinterpreted signs of pain in their dog as calmness, although the ability of trazodone to facilitate behavioral calming and confinement at times distant from the surgery decreased this possibility, as did administration of pain medications during the early postoperative period. In addition, many owners had noted signs of pain in their dogs as a reason for orthopedic evaluation and so were likely able to distinguish signs of pain from the effects of the trazodone. A future randomized, masked, placebo-controlled study could more fully evaluate the critically important placebo effect.

Trazodone appeared to be a safe and useful modulator of behavior at a wide dosage range. Administration of trazodone facilitated confinement and calming during a period of 8 to 12 weeks following elective orthopedic surgery. Presurgery behavioral evaluation of calmness and tolerance of confinement did not predict the final dosage of trazodone required.

References

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Evaluation of thermal antinociceptive effects after intramuscular administration of buprenorphine hydrochloride to American kestrels (Falco sparverius)

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Objective—To evaluate the thermal antinociceptive effects and duration of action of buprenorphine hydrochloride after IM administration to American kestrels (Falco sparverius).

Animals—12 healthy 3-year-old American kestrels.

Procedures—Buprenorphine hydrochloride (0.1, 0.3, and 0.6 mg/kg) and a control treatment (saline [0.9% NaCl] solution) were administered IM in a randomized crossover experimental design. Foot withdrawal response to a thermal stimulus was determined 1 hour before (baseline) and 1.5, 3, and 6 hours after treatment administration. Agitation-sedation scores were determined 3 to 5 minutes before each thermal stimulus. Adverse effects were monitored for 6 hours after treatment administration.

Results—Buprenorphine hydrochloride at 0.1, 0.3, and 0.6 mg/kg, IM, increased thermal threshold for 6 hours, compared with the response for the control treatment. There were no significant differences among buprenorphine treatments. A mild sedative effect was detected at a dose of 0.6 mg of buprenorphine/kg.

Conclusion and Clinical Relevance—at the doses tested, buprenorphine hydrochloride resulted in thermal antinociception in American kestrels for at least 6 hours, which suggested that buprenorphine has analgesic effects in this species. Further studies with longer evaluation periods are needed to fully evaluate the analgesic effects of buprenorphine in American kestrels. (Am J Vet Res 2014;75:1293–1295)