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The use of trazodone to facilitate calm behavior after elective orthopedic surgery in dogs: Results and lessons learned from a clinical trial

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ABSTRACT

Trazodone hydrochloride is an atypical antidepressant that has entered clinical use for dogs and cats for a variety of indications. These include management of anxiety disorders, facilitation of travel and veterinary examinations, and facilitation of calm behavior in hospitalized and postoperative patients. Despite the increasingly common use of trazodone in dogs, very little literature exists evaluating trazodone's efficacy against a placebo control. The aim of the study reported here was to evaluate trazodone in a randomized placebo-controlled clinical trial for use in facilitating calmness and ease of confinement in postoperative dogs. The study enrolled 29 dogs (14 in the trazodone group and 15 in the placebo group) and followed them during 4 postoperative weeks. Trazodone was well tolerated by dogs in the trazodone group. Although dogs in both groups were rated as improved on some behavioral measures, no difference was found between the trazodone and placebo groups in efficacy, with more than 70% of owners in both groups rating the test article (trazodone or placebo) as moderately or extremely helpful for facilitating both calming and crating of their dog. This observed lack of efficacy, over placebo, may be attributed to one or more of several factors that include features about the trial itself and the trial population, a caregiver or placebo-by-proxy effect, a lack of sensitive outcome measures for assessment, or a lack of true efficacy for the medication. It is concluded that future work will be needed to address these factors, and this report aims to provide not only results but lessons learned from the conduct of the described trial.

Introduction

The atypical antidepressant trazodone hydrochloride is currently used by veterinarians for behavioral management in both dogs and cats. Trazodone is classified as a serotonin antagonist/reuptake inhibitor, with reuptake inhibition occurring at higher doses. In humans, trazodone is an antagonist at serotonin 2A and 2C receptors, effectively increasing dopamine and norepinephrine release in the prefrontal cortex, as well as histamine 1 and alpha-1 adrenergic receptors (Stahl, 2013). A recent pharmacokinetics study of oral and intravenously administered trazodone in dogs (Jay et al., 2013) found that trazodone is highly bioavailable after oral dosing and well tolerated at an oral dose of 8 mg/kg. At this dose, authors reported subjective anxiolytic and sedating effects and few adverse events. Trazodone has been evaluated for use in dogs as a single agent (Gruen and Sherman, 2012) and adjunctive therapy in the treatment of canine anxiety disorders (Gruen and Sherman, 2008), as a treatment to facilitate postsurgical calming (Jay et al., 2013; Gruen et al., 2014), and recently as a treatment for stress associated with hospitalization (Gilbert-Gregory et al., 2016). Trazodone has also been suggested to have utility in aiding low-stress handling in dogs (Herron and Shreyer,

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2014). Use in cats is more limited, but trazodone has been shown to be safe in cats (Orlando et al., 2016) and effective at reducing travel anxiety and facilitating veterinary examination (Stevens et al., 2016).

Despite its widespread use and application, most trials using trazodone in dogs have been conducted without a placebo control, thus limiting the scope of the conclusions that can be drawn regarding its efficacy. A previous open trial used trazodone to facilitate postoperative calming in dogs and found that most (89%) of the owners reported moderate or extreme improvement in their dogs with regard to tolerance of confinement and calmness (Gruen et al., 2014). Although this study and others showing sedation and calming in dogs after trazodone administration (Jay et al., 2013; Gilbert-Gregory et al., 2016) are supportive of the effectiveness of trazodone, a placebo control is needed to confirm the findings. In an effort to evaluate the ability of trazodone to facilitate calm behavior after elective orthopedic surgery, a randomized, double-blind, placebo-controlled clinical trial was performed at North Carolina (NC) State University. We hypothesized that dogs receiving trazodone, compared with dogs receiving placebo, would have higher scores for client satisfaction, behavioral calming, tolerance of restriction, and willingness to be controlled on walks. Furthermore, we expected adverse events in both trazodone-treated and placebo-treated cases to be uncommon and mild.

This trial, described in the next sections, did not show efficacy of trazodone over placebo for this use. However, several salient features of the trial may have contributed to this failure. The objectives of this article are to describe the study and its findings, highlight difficulties with performance of the trial, and provide comments regarding the design of future trials.

Methods and materials

All procedures and sample size calculations were approved by the NC State Institutional Animal Care and Use Committee (#13-10-0575) before commencement of the study, and informed consent was obtained from owners of all enrolled dogs. The study aimed to enroll 30 dogs (15 per group) during a period of 6 months. This sample size was based on a priori power calculations using the effect seen in a small pilot study (Gruen et al., 2014), where 15 of 17 dogs showed clinical improvement and what we determined to be a range inclusive of a clinically significant difference. Dogs admitted to the NC State Veterinary Hospital Orthopedic Surgery Service were recruited into this study. Randomization of cases to trazodone or placebo groups and preparation of medication were performed by the NC State Veterinary Pharmacy. Dog owners, veterinarians, technicians, and staff members were blinded to treatment except as noted.

At the time of admission for elective orthopedic surgery, owners were invited to enroll their dogs in the study, and the study protocol was described. The incentives for participation were postoperative laboratory tests (complete blood count and serum biochemistry) at no charge and a $100 reduction in the cost of 8-week postoperative radiographs. Owners who elected to participate signed an informed consent form and were provided with contact information for the study technicians and investigators/veterinarians.

Before surgery, each dog was physically examined by members of the surgery team (directed by SCR), and any recommended screening/preanesthetic laboratory tests were performed, typically a complete blood count and serum biochemistry panel. After surgery, all dogs had the following standard prescription regimen: days 1-10, daily nonsteroidal anti-inflammatory; days 1-7, oral tramadol (4-6 mg/kg/q12 hours); and days 1-7, half dose of test article (either trazodone at 3-5 mg/kg/q12 hours, or an equivalent tablet size and quantity of placebo given q12 hours). This starting dose reduction of the test article was standard practice at our hospital to address concerns about the potential for excessive serotonin levels with concurrent use of tramadol and trazodone (Gwaltney-Brant et al., 2000). After day 7, when tramadol was discontinued, the dose of the test article was increased to the assigned level (trazodone at 5-7 mg/kg/q12 hours or an equivalent tablet size and quantity of placebo given q12 hours). Administration of the test article continued for 4 weeks after surgery, with dosage subject to change if a rescue strategy was needed. Several rescue strategies regarding the trazodone/placebo were anticipated and would be used, as needed, without releasing the blinding: (1) If the dose of the test article seemed too high for an individual animal (e.g., resulting in excessive sleepiness), in consultation with the investigators and pharmacy, the dose could be decreased; (2) if the client reported lack of efficacy, in consultation with the investigators and pharmacy, the dose of the test article could be increased; (3) if the client reported lack of efficacy and was, as a consequence, considering withdrawal from the study because of lack of efficacy, then the test article the dog received (trazodone or placebo) would be stopped, and known trazodone would be dispensed for the duration of the study.

Behavioral measures

Owners of dogs participating in the study completed a presurgical questionnaire on their dogs' baseline behavioral profile, including baseline activity level, control of leash walks, and tolerance for confinement. After surgery, dog owners were given, in writing, standardized postoperative instructions for confinement and activity restriction for 4 weeks after surgery. During this postoperative confinement period, the test article (either trazodone or placebo) was to be administered twice daily. Each week, owners were sent, via electronic mail, the link to an online questionnaire (see Supplemental Materials section) regarding their dog's tolerance of confinement and activity restriction, willingness to be controlled on leash walks, and overall activity level. Additional questions confirmed dosing schedule, adverse events related to medication administration, and client satisfaction. The study technician called for follow up with any owner who did not return the questionnaire in a timely manner. The study technician also called dog owners after 4 weeks on study. At that time, owners could elect to continue to administer test article for up to 8 weeks. At the 8-week postsurgery visit, postoperative radiographs were taken, laboratory tests (complete blood count and chemistry profile) were performed, and results were compared with the presurgery laboratory values.

Statistical analyses

Demographic characteristics of dogs in the trazodone and placebo groups were compared using *t* tests for weight and age and Fisher exact test for sex distribution. Responses to Likert scales for behavioral outcomes were converted to ordinal numerical rating scales, where lower scores were always for more desired behaviors (see Supplemental Materials section for key). Baseline scores and change from baseline scores were compared between groups using Wilcoxon 2-sample tests. Overall improvement (in both groups) was compared with baseline using Wilcoxon signed rank tests. Final dosages (the dosages reported by owners at the 4-week follow-up survey) were compared between groups using *t* tests. Pre- and postoperative laboratory work results were compared for each patient, and any clinically significant changes were reported.

Results

Animals

During 10.5 months, 29 dogs admitted to the veterinary hospital for orthopedic surgery were enrolled in the study. Demographic data for dogs in both groups are shown in Table 1. No differences

Table 1
Demographic data for enrolled dogs in each group

Treatment group	N	Age (y; mean ± SD)	Weight (kg; mean ± SD)	Sex (M/MC/F/FS)
Trazodone	14	4.50 ± 2.47	29.13 ± 3.20	0/4/1/9
Placebo	15	4.47 ± 3.07	29.46 ± 2.31	1/5/1/8

SD, standard deviation; M, male; MC, male castrate; F, female; FS, spayed female. For sex, totals are given for M, MC, F, and FS. Age and weight are shown as mean ± standard error.

were found between the trazodone and placebo groups for the distribution of sexes (Fisher exact test, $P = 1.00$), mean age ($t = -0.03$; $P = 0.97$), or mean weight ($t = 0.08$; $P = 0.93$). Surgeries performed included stabilization of the stifle (n = 23), fracture repair/external fixator placement (n = 5), and total hip replacement (n = 1). There was no difference between the trazodone and placebo groups in the distribution of surgery types by location (stifle, hip, or other; Fisher exact test, $P = 1.00$). Twenty-five of the 29 dogs enrolled completed the study, with 3 dogs in the trazodone group and 1 in the placebo group being withdrawn and excluded from the analysis of efficacy. Data from all dogs were used for reporting on safety.

Dose range and behavioral outcomes

The final dosage range dogs received ranged from 5.6 to 21.6 mg/kg/day with a mean ± standard error of the mean of 15.13 ± 1.6 mg/kg/day (divided into twice-daily dosing). There was no difference between the trazodone and the placebo groups in the mean final dosage (t test, $t = -0.30$; $P = 0.77$). At the 4-week time point, most owners in both the trazodone (100%; 11 of 11) and placebo (85.7%, 12 of 14) groups elected to continue the assigned test article at the assigned dose.

No significant differences were found between the trazodone and placebo groups in baseline ratings of greeting behavior ($P = 0.21$), calmness ($P = 0.15$), willingness to be controlled on leash ($P = 0.86$), pulling ($P = 0.53$), or tolerance of confinement at home ($P = 0.68$). See Table 2 for medians and interquartile ranges.

No significant differences were found between the trazodone and placebo groups in the change in rating for greeting behavior ($P = 0.69$), calmness ($P = 0.39$), willingness to be controlled on leash ($P = 0.69$), pulling ($P = 0.12$), or tolerance of confinement at home ($P = 0.68$). See Table 3 for medians and interquartile ranges.

Owner ratings of the efficacy of test article were high in each group, with 78.6% (11 of 14) of owners reporting that the test article was moderately or extremely helpful for facilitating calming in the placebo group and 72.7% (8 of 11) in the trazodone group. Similarly, for facilitating crating, 71.4% (10 of 14) of owners in the placebo group and 81.8% (9 of 11) in the trazodone group reported that the test article was moderately or extremely helpful. Among owners who reported an effect of the test article, there was neither difference in duration of effect between trazodone and placebo groups ($P = 0.84$) nor a noted change in effect over time ($P = 0.62$). Similarly, among owners who reported an effect of the test article, there was neither difference in the reported duration of efficacy between trazodone and placebo groups ($P = 0.48$) nor a change over time ($P = 0.49$).

Owners of 3 dogs in each group (21.4% for placebo and 27.3% for trazodone) requested a rescue with known trazodone during the trial. After the rescue, owners of 5 of 6 dogs (including 2 that had been receiving trazodone) reported that the trazodone was moderately or extremely helpful for facilitating calming and crating in their dog.

Table 2
Medians and interquartile ranges for ratings of baseline behaviors in dogs in the placebo and trazodone groups

Treatment group	N	Median	Lower quartile	Upper quartile
Greeting				
Placebo	14	3.0	2.0	3.0
Trazodone	11	3.0	2.0	4.0
Calmness				
Placebo	14	2.0	1.0	3.0
Trazodone	11	2.0	2.0	4.0
Willingness to be controlled on leash				
Placebo	13	1.0	0.0	2.0
Trazodone	11	1.0	0.0	2.0
Pulling				
Placebo	14	1.0	1.0	2.0
Trazodone	11	2.0	1.0	3.0
Tolerance of confinement at home				
Placebo	14	2.0	0.0	2.0
Trazodone	11	2.0	0.0	2.0

No significant differences were found between groups for any variables.

Table 3
Medians and interquartile ranges for the change in behavioral scores for dogs from baseline to their final survey

Treatment group	N	Median	Lower quartile	Upper quartile	*P* for overall improvement
Greeting					
Placebo	14	−0.5	−1.0	0.0	**0.003**
Trazodone	11	−1.0	−2.0	0.0	
Calmness					
Placebo	14	0.0	−1.0	1.0	0.063
Trazodone	11	−1.0	−2.0	0.0	
Willingness to be controlled on leash					
Placebo	12	0.0	−1.5	0.5	0.31
Trazodone	10	0.0	−1.0	1.0	
Pulling					
Placebo	12	−0.5	−1.0	0.0	0.39
Trazodone	11	0.0	−1.0	1.0	
Tolerance of confinement at home					
Placebo	14	0.0	0.0	2.0	**0.002**
Trazodone	11	0.0	0.0	2.0	

A negative score indicates improvement for the variable. No significant differences in change in behavior were found between groups for any of the variables. Significant improvements from baseline were found overall (in both groups) for greeting and tolerance of confinement at home (in bold).

Safety and adverse events

No clinically significant changes in laboratory parameters were found in either the placebo or the trazodone groups. With the exception of 1 dog, described in the next paragraph, no adverse events were noted for dogs in either the placebo or the trazodone groups.

A 4.5-year-old male castrated Labrador retriever was withdrawn from the study when he was diagnosed with Addison's disease 1 week after triple tibial osteotomy surgery to stabilize his stifle after complete tear of the cranial cruciate ligament. The dog was enrolled in the study and underwent routine presurgical physical examination and routine laboratory work (packed cell volume = 35%; total protein = 7.2 g/dL; glucose = 136 mg/dL; and blood urea nitrogen = 30-40 mg/dL). After surgery was performed, the dog returned home. The test article (trazodone) was given at half dose for the 1-week period according to the study protocol. Based on owner concern about the dog's postoperative sleepiness and decreased appetite, the dog was presented to the referring veterinarian for evaluation. A diagnosis of hypoadrenocorticism was made, and the dog was withdrawn from the study.

Discussion

As in previous reports, trazodone was well tolerated, over a wide dosage range, with no noted adverse events attributed to drug administration. In this study, most dog owners reported

improvement in their dog's behavior with administration of the test article, with no difference in time to or duration of effect between groups. Treatment with trazodone during the postoperative period failed to show efficacy over placebo for facilitating calm greeting behavior, overall calmness, willingness to be controlled on a leash, and tolerance of confinement at home. These results were surprising, particularly given the ubiquity of the use of trazodone in our hospital, and the results from a similarly conducted open-label trial (Gruen et al., 2014). This observed lack of efficacy, over placebo, may be attributed to 1 or more of several factors that include features about the trial itself and the trial population, a caregiver or placebo-by-proxy effect, a lack of sensitive outcome measures for assessment, or a lack of true efficacy for the medication.

Regarding the trial and trial population, systematic bias may have existed as the use of trazodone for postsurgical confinement was common practice in our hospital. Before the initiation of the trial, surgeons were already convinced of the efficacy of trazodone, despite a lack of placebo-controlled evidence and were hesitant to enroll their own patients in the trial, resulting in a protracted recruitment period and failure to reach the targeted number of cases. Although difficult to assess, it is possible that case selection was already biased toward cases that were calmer and more accepting of confinement before surgery. This is reflected in the low preoperative scores for calmness and sluggish recruitment rate (29 dogs during 10.5 months, despite an orthopedic caseload of 255 cases during that period). However, this bias could not be confirmed without surveying all patients presenting to the orthopedic surgery service during the study period, and this was not done. Future studies would benefit from being performed in a setting where the medication under study was relatively new or uncommonly used in practice, and pre-existing beliefs regarding efficacy were low. An alternative approach would be to have an independent process for enrolling cases that does not involve clinicians in the enrollment or consent.

These pre-existing beliefs and the potential for these to have been conveyed to owners and/or caregivers may also have contributed to the caregiver placebo effect seen in this study, although standardized information and instructions were provided to all participants. As noted by Overall and Dunham (2009), an owner's enrollment in a clinical trial is an assessment of perceived risk versus benefit. Those who choose to participate must decide that there would be a positive effect of the trial medication or that the risk from no effect would be low. A placebo is thus used to control for the effect of anticipation or participation that contributes to a caregiver placebo effect as well as the effects of participating in a trial. The caregiver placebo effect may be defined as a perceived benefit to a patient, as reported by the owner and/or caregiver, while the patient was receiving a placebo. This effect is not unique to this trial and has been noted in studies of other treatments for orthopedic disease (Conzemius and Evans, 2012; Malek et al., 2012; Gruen et al., 2017) as well as trials for behavioral therapies (King et al., 2000; Simpson et al., 2007; Cottam and Dodman, 2009). Strictly speaking, the caregiver placebo effect on subjective outcome measures, as reported by the owner and/or caregiver, would be accompanied by a lack of significant improvement on an objective outcome measure (Conzemius and Evans, 2012).

There is also the potential for a placebo-by-proxy effect to be playing a role in the results presented here. In the placebo-by-proxy effect, the belief of the owners that their dog is receiving a medication that facilitates calm behavior could change the way that the owner interacts with the dog and could lead to an actual change in the dog's behavior because of this interaction. Although not called by the same term, this idea was also discussed in a study by Cottam et al. (2013) that evaluated the efficacy of an antistatic cape for the treatment of thunderstorm anxiety in dogs. In that study, both the lined cape and the unlined (placebo) cape resulted in improvement on a global assessment of dogs' behavior. The authors postulated that one contributing cause could be a change in owner expectations and thus their body language and behavior, resulting in a change in the dogs' behavior (Cottam and Dodman, 2009).

Regardless of its true effect on the dogs in the study, the belief system of the owners clearly had an effect on owner ratings. Cases that highlight this include the 3 cases in the trazodone group where owners requested known trazodone because of their perception that their dog was not benefiting from the unknown medication. This was done without breaking the blind, and 2 of these owners went on to rate the trazodone as moderately or extremely effective for their dog. In one of these cases, the dog had already had a dosage increase of the test article (trazodone), as per the rescue protocol, with no improvement. When the dog was switched to known trazodone, it was prescribed at the initial target dosage (i.e., lower than what the dog had been receiving just before the rescue). Despite this, once the dog was on known trazodone, this owner's view of the efficacy of trazodone changed.

Other possible causes for the lack of efficacy over placebo seen in this trial include that the study was underpowered or that the outcome assessment tool used for this study was not sensitive enough to capture the differences between the groups. Based on the results of our clinical experience and a small pilot study (reported previously [Gruen et al., 2014]), we expected a strong positive effect of the trazodone on measures of calming, and our power analysis suggested that 30 dogs would be sufficient for the effect size we expected in the study. We did not anticipate that the placebo would also show a profound positive effect (with more than 70% of owners in the placebo group indicating utility for facilitating calming and crating), and thus our sample size was calculated without the potential for such a small difference between the trazodone and placebo. This lack of power to detect a small difference could explain some, but not all, of our reported findings. The outcome tool that we used, the survey of the owners, was identical to that used in both the pilot and the previously reported open-label trial (Gruen et al., 2014). Although suitable for showing improvement in these trials, this outcome assessment tool may not have been sensitive enough for use in this placebo-controlled trial. This assessment tool was subject to a flaw that affects many tools in that, despite incorporating feedback from owners, it was largely based on the investigators' assumptions of what would change with administration of trazodone. This provided the instrument with high face validity, that is, that it looked like it would measure the outcome of interest. However, the instrument itself could have been improved by an objective review of behavioral effects of trazodone administration and systematic assessment of responsiveness and validation (e.g., Boynton and Greenhalgh, 2004; Zamprogno et al., 2010; Klinck et al., 2015; for review). This is particularly important when signs are nonspecific (Overall and Dunham, 2009) and when an instrument serves as the primary outcome measure for a trial. This is an area where much research is needed. The present study would have benefited from the inclusion of objective or quantifiable measures. Video of dogs in their confinement spaces would have provided quantifiable behaviors; however, dogs were not typically confined before surgery, making change from baseline difficult to assess. Alternatively, our instrument could have included questions regarding more specific behaviors as in a recent study evaluating the use of dexmedetomidine

oromucosal gel in dogs with fireworks (noise)-associated acute anxiety (Korpivaara et al., 2017).

Finally, the possibility exists that trazodone is not actually any more effective than placebo as a medication to facilitate calming during the postoperative period. Although this runs contrary to the beliefs of the investigators, the results of this study cannot disprove this point. Indeed, only 1 study of trazodone use in dogs or cats has shown efficacy over a placebo for a behavioral indication (Stevens et al., 2016). Trazodone's mechanism of action is dose dependent; at lower doses, trazodone primarily acts as a serotonin 2A receptor antagonist, with antihistaminergic and antialpha$_1$ adrenergic activity. At higher doses, trazodone also acts as a serotonin 2C antagonist and serotonin reuptake inhibitor; these dosage breakpoints have not been established in dogs. However, an oral dosage of 8 mg/kg produced plasma concentrations within the therapeutic (antidepressant) range for humans (Jay et al., 2013). Trazodone is commonly used as an adjunctive medication, in both human and veterinary medicine, for its synergistic effects with other antidepressants. As a single agent, trazodone may be most useful as a hypnotic (Stahl, 2013), and refinement of study instruments could better allow separation of mild sedation versus anxiolysis. For the present study, where calming and tolerance of confinement were the target outcomes, this distinction is less pressing; the same is not true for other indications. Further research into the efficacy of trazodone for the postoperative period and other behavioral indications is needed, especially given the growing use of trazodone in veterinary medicine (Jay et al., 2013; Gilbert-Gregory et al., 2016). It is our recommendation that these studies be powered to account for a high placebo effect, conducted using reliable and validated outcome assessments, and performed at institutions where widespread trazodone use is not already in place. This would allow clinical studies such as this to meet the highest criteria as for an Food and Drug Administration study. We acknowledge that when the cost of failure is high, such as with a surgical repair, the use of a placebo may lead to nonrandom selection of patients for inclusion into a trial and further suggest that trazodone may need to be compared with an institution's standard of care medication. Indeed, it was dissatisfaction with the standard-of-care option, acepromazine, that led to the initiation of the use of trazodone at our institution.

In conclusion, this study found that trazodone was well tolerated by dogs and was rated as effective by owners for facilitating calming and crating during the postoperative period. However, it failed to show efficacy superior to a placebo, and we do not know whether this is because it is ineffective or our study was inadequate to detect efficacy. If management of owner expectations could lead to the same reporting of calmness during the postoperative period, without the need for medication, this would be an important clinical result. There is a need for further research into the efficacy of trazodone for use in dogs and into the definitions, characterizations, and effects of placebos as interventions.

Conflict of interest

The authors declare no conflict of interest.

Authorship

The idea for the article was conceived by Drs. Gruen, Roe, and Sherman. The experiments were designed by Drs. Gruen, Roe, and Sherman. The experiments were performed by Drs. Roe and Sherman. The data were analyzed by Dr. Griffith. The article was written by Dr. Gruen and edited by Drs. Roe, Griffith, and Sherman.

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Supplementary data

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