ACEPROMAZINE IS COMMONLY USED IN VETERINARY MEDICINE AS A SEDATIVE AND TRANQUILIZER. UNTIL RECENTLY, ACEPROMAZINE WAS CONSIDERED TO HAVE ANXIOLYTIC PROPERTIES, ESPECIALLY WHEN PAIRED WITH AN OPIOID. 1–3 HOWEVER, FURTHER KNOWLEDGE OF THE PHARMACOLOGICAL ACTIVITY OF THE DRUG CLASSIFIES ITS ACTIONS AS A TRANQUILIZER RATHER THAN AN ANXIOLYTIC.4 THE SEARCH FOR DRUGS TO COUNTER ANXIETY OR PHOBIAS AND TO IMPROVE THE EXPERIENCE OF TRAVEL BY CAR OR AIRPLANE FOR SOME PETS HAS LED VETERINARY BEHAVIORISTS TO EXPLORE THE BENEFICIAL EFFECTS OF DRUGS SUCH AS TRAZODONE. TRAZODONE IS A SEROTONIN RECEPTOR ANTAGONIST AND REUPTAKE INHIBITOR THAT BINDS TO AND ANTAGONIZES 5-HT2A RECEPTORS.5,6 THIS MECHANISM OF ACTION PLACES THE DRUG IN THE CATEGORY OF ATYPICAL ANTIDEPRESSANT MEDICATIONS. THE DRUG ALSO CAUSES SOME α1-ADRENERGIC RECEPTOR BLOCKADE, WHICH CAN CAUSE VASODILATORY EFFECTS SIMILAR TO THOSE INDUCED BY ACEPROMAZINE.7 THE ANXIOLYTIC PROPERTIES OF TRAZODONE SEEM TO BE RELATED TO THE RECEPTOR SITE ACTIVITIES OF THE DRUG, WHICH ALTER SEROTONIN AND LIKELY REDUCE γ-AMINOBUTYRIC ACID CONCENTRATIONS IN THE CEREBRAL CORTEX.6,8

OBJECTIVE
To compare the doses of propofol required to induce general anesthesia in dogs premedicated with acepromazine maleate or trazodone hydrochloride and compare the effects of these premedicants on cardiovascular variables in dogs anesthetized for orthopedic surgery.

DESIGN
Prospective, randomized study.

ANIMALS
30 systemically healthy client-owned dogs.

PROCEDURES
15 dogs received acepromazine (0.01 to 0.03 mg/kg [0.005 to 0.014 mg/lb], IM) 30 minutes before anesthetic induction and 15 received trazodone (5 mg/kg [2.27 mg/lb] for patients > 10 kg or 7 mg/kg [3.18 mg/lb] for patients ≤ 10 kg, PO) 2 hours before induction. Both groups received morphine sulfate (1 mg/kg [0.45 mg/lb], IM) 30 minutes before induction. Anesthesia was induced with propofol (4 to 6 mg/kg [1.82 to 2.73 mg/lb], IV, to effect) and maintained with isoflurane or sevoflurane in oxygen. Bupivacaine (0.5 mg/kg [0.227 mg/lb]) and morphine (0.1 mg/kg [0.045 mg/lb]) were administered epidurally. Dogs underwent tibial plateau leveling osteotomy (n = 22) or tibial tuberosity advancement (8) and were monitored throughout anesthesia. Propofol induction doses and cardiovascular variables (heart rate and systemic, mean, and diastolic arterial blood pressures) were compared between groups.

RESULTS
The mean dose of propofol required for anesthetic induction and all cardiovascular variables evaluated did not differ between groups. Intraoperative hypotension developed in 6 and 5 dogs of the acepromazine and trazodone groups, respectively; bradycardia requiring intervention developed in 3 dogs/group. One dog that received trazodone had priapism 24 hours later and was treated successfully. No other adverse effects were reported.

CONCLUSIONS AND CLINICAL RELEVANCE
At the described dosages, cardiovascular effects of trazodone were similar to those of acepromazine in healthy dogs undergoing anesthesia for orthopedic surgery. (J Am Vet Med Assoc 2017;250:408–416)
Drugs available for the treatment of dogs with signs of anxiety in a clinical setting where anesthesia is required are limited. Options include \(\alpha_2\)-adrenergic receptor agonists, benzodiazepines, and the controversial phenothiazines, each of which can cause substantial dose-dependent sedation and side effects. The \(\alpha_2\)-adrenergic receptor agonists can have considerable cardiovascular effects, such as decreases in cardiac output and cardiac index and increases in systemic vascular resistance index and central venous pressure.\(^1,9\) Because of these effects, drugs of this class are recommended primarily for sedation in healthy patients only. Benzodiazepines can produce dysphoria, agitation, and excitement, which make this drug class a poor choice for premedication of an anxious, albeit healthy, patient.\(^1,10\) Phenothiazines are known for their vasodilatory effects and are associated with loss of thermoregulatory control, \(\alpha_2\)-adrenergic and dopaminergic receptor antagonism, and behavioral disinhibition.\(^1\)

A benefit of trazodone is that, similar to acepromazine, it can be orally administered. This option makes it an attractive treatment choice for postoperative sedation in dogs and also for use in dogs needing routine postoperative visits that have signs of fear or apprehension associated with the hospital or with travel by car, because the drug can be given by the client at home.\(^11\) In the authors’ experience, an increasing number of patients have been seen by the anesthesia service after having been prescribed trazodone. However, relatively little information exists in the literature regarding the safety and efficacy of this drug in small animals from a clinical standpoint.

To our knowledge, the effects of orally administered trazodone as a premedication in dogs undergoing general anesthesia have not been reported. The purpose of the study reported here was to compare the doses of propofol needed to induce general anesthesia in dogs premedicated with acepromazine or trazodone and to compare the effects of these 2 premedicants on cardiovascular variables in dogs undergoing anesthesia and orthopedic surgery. We hypothesized that the dose of propofol required for anesthetic induction would be similar between dogs premedicated with trazodone or acepromazine. We also hypothesized that the incidence of hypotension in dogs administered trazodone would be similar to that in dogs that received acepromazine but that the severity of hypotension would be less in the former group.

**Materials and Methods**

**Animals**

This study was performed in conjunction with another study performed by staff of the Behavior Service at the University of Minnesota College of Veterinary Medicine. Thirty client-owned dogs (number selected on the basis of a power analysis for the concurrent study) were recruited for use in the present study. Dogs having a deficiency in the cranial cruciate ligament necessitating surgical intervention by means of TPLO or TTA and deemed healthy on the basis of physical examination (including preoperative CBC and serum biochemical analysis) were included in the study. The TPLO and TTA procedures were chosen because these were frequently performed in the hospital where the study took place. Exclusion criteria included a previous seizure history or history of treatment with \(\geq 1\) of the following medications: fluconazole, itraconazole, or ketoconazole within the previous 2 weeks; quinolones within the previous 2 days; amitraz products within the previous 4 weeks; monoamine oxidase inhibitors within the previous 4 weeks; antidepressants within the previous 2 months; glucocorticoids within the previous 2 weeks; or herbal products within the previous 2 weeks. Dogs that had received tramadol were included after a washout period of 12 hours. Drug withdrawal times were calculated as \(\geq 5\) times the half-life of a given product.\(^3,12\) The study was approved by the University of Minnesota Institutional Animal Care and Use Committee. Informed client consent was obtained prior to enrollment of any dog in the study.

**Procedures**

Food was withheld for 12 hours prior to anesthetic induction. Dogs underwent a preoperative physical examination that included measurement of heart and respiratory rates and body temperature (recorded as baseline values). Dogs were assigned to 1 of 2 treatment groups by use of a computerized randomization program. One group (\(n = 15\)) received acepromazine maleate\(^3\) (0.01, 0.02, or 0.03 mg/kg [0.005, 0.009, or 0.014 mg/lb], IM) and morphine sulfate\(^6\) (1 mg/kg [0.45 mg/lb], IM) 30 minutes prior to induction of anesthesia. The dose of acepromazine was determined on the basis of the anesthesiologist’s preference and the demeanor of the dog. The other group (\(n = 15\)) received trazodone hydrochloride\(^3\) (5 mg/kg [2.27 mg/lb] for patients > 10 kg [4.5 lb] or 7 mg/kg [3.18 mg/lb] for patients \(\leq 10\) kg, PO) 2 hours prior to induction; this group also received morphine (1 mg/kg, IM) 30 minutes prior to induction. The dose of trazodone was extrapolated from a previous study\(^13\) and determined on the basis of clinical experience of Behavior Service staff. Actual doses administered were rounded to the nearest quarter tablet (50-mg tablet strength).

Propofol\(^6\) (4 to 6 mg/kg [1.8 to 2.7 mg/lb], IV, to effect) was manually administered over 20 to 30 seconds with the dog positioned in sternal recumbency. Jaw tone, palpebral reflex, and reaction to touching the tongue with the laryngoscope blade were assessed to determine whether a sufficient plane of anesthesia allowing for orotracheal intubation was reached. Personnel administering anesthetics were not otherwise involved in the study and were aware of the study treatment groups; they were not informed that propofol dose was being evaluated in the study. Anesthesia was maintained with isoflurane\(^6\) or sevoflurane\(^6\) delivered in 100% oxygen via a precision vaporizer\(^6\) in a semiclosed circle system. Dogs were manually ventilated and mechanical ventilation\(^6\) was instituted as necessary to maintain end-tidal partial pressure of CO\(_2\) between 35 and 45 mm Hg. Tidal volume was maintained between 10 and 20 mL/kg (4.5 and 9 mL/lb) and peak inspiratory pressure between 10 and 40 cm Hg.
20 cm H₂O. Lactated Ringer solution was administered IV throughout the anesthetic episode at 10 mL/kg/h.

Monitoring included continuous assessment of heart and respiratory rates and mucous membrane color (recorded every 5 minutes). Oxygen saturation of hemoglobin measured by pulse oximetry (with the sensor placed on the patient’s tongue), side-stream end tidal partial pressure of CO₂, ECG output (bipolar limb lead placement; lead II), and body temperature (measured with an esophageal probe) were also continuously monitored (recorded every 15 minutes). Intermittent monitoring included anesthetic depth (every 5 to 15 minutes; determined by jaw tone, eye position, palpebral reflex, and cardiovascular and respiratory values), noninvasive blood pressure measurement with an oscillometric device with an appropriately sized cuff (every 5 minutes until direct blood pressure monitoring began), and capillary refill time (every 15 minutes). Individuals monitoring the dogs were not blinded to the treatment group assignments.

After anesthetic induction, preoperative radiographs were obtained and dogs were placed in sternal recumbency for lumbosacral epidural anesthetic administration with an aseptic technique. The area over the lumbosacral space was clipped and cleansed with a betadine solution. The medications were administered via a dilution to a total volume of sterile water. The medications were administered with an oscillometric device with an appropriately sized cuff (every 5 minutes until direct blood pressure monitoring began), and capillary refill time (every 15 minutes). Individuals monitoring the dogs were not blinded to the treatment group assignments.

After anesthetic induction, preoperative radiographs were obtained and dogs were placed in sternal recumbency for lumbosacral epidural anesthetic administration with an aseptic technique. The area over the lumbosacral space was clipped and cleansed with a betadine scrub. Preservative-free morphine (0.1 mg/kg [0.045 mg/lb]) and bupivacaine (0.5 mg/kg [0.23 mg/lb]) were diluted to a total volume ≤ 0.2 mL/kg (0.09 mL/lb) with sterile water. The medications were administered via a 22-gauge, 2.5- to 3.5-inch (63- to 90-mm; as appropriate) spinal needle with a Quincke-type bevel.

The hanging drop method was used in combination with the lack-of-resistance technique.

Dogs were then placed in lateral recumbency and an over-the-needle arterial catheter was preferentially placed in a palmar artery for direct arterial blood pressure measurements. If attempts to catheterize a palmar artery were unsuccessful, the catheter was placed in the dorsal pedal artery of the limb contralateral to that undergoing surgery.

Dogs were moved to the surgical suite and noninvasive blood pressure monitoring was transitioned to invasive blood pressure monitoring with a factory-calibrated multiparameter monitor. The arterial catheter was connected to a commercial pressure transducer placed at the level of the right atrium and zeroed prior to the first measurement in accordance with the manufacturer’s recommendations. A container of heparinized saline (0.9% NaCl) solution (7 U of heparin/mL) was attached to the pressure transducer, and a constant flow of the solution (3 mL/h) was delivered through the catheter to maintain patency. Once direct blood pressure measurement was established, the SAP, MAP, and DAP were monitored continuously and recorded every 5 minutes. Other physiologic variables continued to be monitored as described. Body temperature was maintained within 37.0° to 39.0°C (98.6°F to 102.2°F) with a forced-air warming device and over-the-body blanket. Cardiovascular variables were considered normal if the heart rate was 60 to 120 beats/min, SAP was 90 to 160 mm Hg, and MAP was 60 to 100 mm Hg. For study purposes, patients were classified as having intraoperative hypotension if treatment measures (eg, fluid bolus or medication) were required to address MAP < 60 mm Hg. Adjustments in delivered inhalation anesthesia percentage were performed when indicated to maintain an appropriate plane of anesthesia, which was determined by ventromedial eye position, slight to no palpebral reflex, and moderate jaw tone, in addition to sudden changes in cardiovascular and respiratory variables indicative of nociceptive stimulation or inadequate anesthetic depth. A constant rate infusion of dobutamine or dopamine was initiated if MAP became < 60 mm Hg and the patient did not respond to bolus administration of lactated Ringer solution (10 mL/kg) or decrease in the percentage of inhalation anesthetic. Inotropic agents were selected on the basis of individual patient assessment. If the heart rate became < 60 beats/min and MAP was < 60 mm Hg, glycopyrrolate (0.005 mg/kg [0.002 mg/lb], IV) was administered.

Dogs underwent TPLO or TTA as determined by surgeon preference. The procedures had a similar surgical approach and both required osteotomy and screw placement and were expected to produce similar degrees of surgical stimulation. In the event that patients required additional analgesic administration to manage intraoperative surgical stimulation as perceived by the anesthetist, dogs were treated with a 1:2 mixture of oxygen:nitrous oxide or with a bolus or constant rate infusion of an analgesic agent (eg, hydromorphone, 0.05 mg/kg [0.023 mg/lb]; fentanyl, 10 μg/kg/h [0.002 mg/lb]; lidocaine, 4 mg/kg/h; ketamine, 0.5 mg/kg/h; or morphine 0.1 mg/kg/h). Dosages were as determined by the anesthetist; approximate values are provided.

For study purposes, the duration of anesthesia was measured from the time of induction (time 0) to the discontinuation of inhalation anesthetic. The duration of surgery was measured from the time of incision (time 0) to the time of placement of the last suture.

Postoperative recovery

After surgery ended and the final cardiovascular variables were recorded, data gathering for the present study ended. The dogs underwent postoperative radiography and were monitored throughout the recovery process. Behavioral data were collected for the parallel study that was being performed.

Statistical analysis

Distributions for age, body weight, the dose of propofol required to achieve endotracheal intubation, vaporizer dial setting, duration of anesthesia and surgery, heart rate, SAP, MAP, and DAP of dogs in the acepromazine and trazadone treatment groups were assessed with a D’Agostino-Pearson test. All variables were normally distributed except for age and duration of surgery. Body weight, dose of propofol, vaporizer setting, and anesthetic time were compared by use of 2-sample t tests, and age and surgery time were compared by Mann-Whitney U tests. A 2-way repeated measures ANOVA was used to compare cardiovascular variables between groups, with
time and treatment (acepromazine or trazodone) as independent variables. For heart rate comparisons, only data from 5 to 125 minutes after induction were included in the analysis, owing to a limited number of dogs under general anesthesia after this period. The incidence rate of hypotension in the acepromazine and trazodone groups was compared with the Fisher exact test. Only dogs that had direct blood pressure monitoring data were included in analysis of SAP, MAP, and DAP, and only data recorded from the time of arterial catheter placement to the last time point at which data were available for all dogs with arterial catheters (115 minutes) were included. A Bonferroni correction for multiple comparisons was used when significant differences were found.

To determine the effect of inotropic agents on cardiovascular variables, a 2-way ANOVA was used to compare differences between groups with study treatment (acepromazine or trazodone) and inotrope as independent variables. Because most dogs received inotropes for a short period of time, the cardiovascular data collected during this time were recorded, and the mean for each variable was calculated for inotrope-treated dogs and compared between groups. All dogs were included in this analysis for heart rate, but only dogs with direct blood pressure monitoring were included when SAP, MAP, and DAP were compared.

All analyses were carried out with commercially available statistical software. Parametric values were expressed as mean ± SD, and nonparametric values were expressed as median (IQR). Values of \( P < 0.05 \) were considered significant.

A retrospective power analysis was performed because the project was part of another study. For this analysis, heart rate, SAP, MAP, and DAP data were evaluated, and the \( \alpha \) value was set at 0.05 with 80% power.

Results

The 30 study dogs included 17 females (13 spayed and 4 sexually intact) and 13 males (all neutered). Breeds included Labrador Retriever (n = 7), mixed breed (6), Golden Retriever (3), Cairn Terrier (2), German Shepherd Dog (2), Newfoundland (2), and 1 each of 8 other breeds. Median age of the dogs was 5 years (IQR, 2 to 11.7 years) and mean ± SD weight was 34.42 ± 11.43 kg (75.72 ± 25.15 lb). Most dogs (n = 22) underwent TPLO (right-sided in 13, left-sided in 8, and bilateral in 1). The remainder (n = 8) underwent TTA (4 right-sided and 4 left-sided).

The median ages of dogs in the acepromazine group (6.0 years; IQR, 4.0 to 7.0 years [n = 15]) and in the trazodone group (4.3 years; IQR, 3.0 to 5.8 years [15]) were not significantly (\( P = 0.10 \)) different. Mean ± SD body weights were also similar between groups (34.7 ± 9.8 kg [76.34 ± 21.56 lb] and 34.1 ± 13.2 kg [75.02 ± 29.04 lb] for the acepromazine and trazodone groups, respectively; \( P = 0.88 \)).

In the acepromazine group, 7 dogs received acepromazine at 0.01 mg/kg, 5 at 0.02 mg/kg, and 3 at 0.03 mg/kg. In the trazodone group, 14 dogs received the 5 mg/kg dose of trazodone, and 1 received the 7 mg/kg dose. The mean ± SD propofol dose for the acepromazine group was 3.5 ± 0.9 mg/kg, compared with 3.9 ± 1.3 mg/kg for the trazodone group (\( P = 0.33 \)). All dogs were orotracheally intubated successfully, and no complications were observed during induction of anesthesia. Only 2 dogs (both in the acepromazine group) received sevoflurane; the mean ± SD vaporizer setting was 2.8 ± 0.3% for these dogs. The mean ± SD vaporizer settings for dogs that received isoflurane in the acepromazine (1.6 ± 0.3%; n = 13) and trazodone (1.7 ± 0.3%; 15) groups did not differ significantly (\( P = 0.50 \)). Durations of anesthesia (mean ± SD, 200 ± 48 minutes vs 182 ± 28 minutes for the acepromazine and trazodone groups, respectively; \( P = 0.21 \)) and surgery (median, 65 minutes [IQR, 55 to 120 minutes] vs 70 minutes [IQR, 55 to 90 minutes], respectively; \( P = 0.72 \)) were also similar between groups.

Arterial catheter placement was attempted in all dogs approximately 45 minutes after induction of general anesthesia. Arterial catheters were used successfully in 26 of 30 dogs (12 and 14 in the acepromazine and trazodone groups, respectively). Seventeen of the catheters...
were placed in a palmar artery and 9 were placed in a dorsal pedal artery. For 3 dogs, attempts to place an arterial catheter were unsuccessful, and in 1 dog, the catheter was placed successfully but was not patent once connected to the transducer in the operating room. Blood pressures were measured noninvasively throughout surgery for these 4 dogs, which were excluded from analyses of SAP, MAP, and DAP.

Mean ± SD cardiovascular variables for the acepromazine and trazodone groups were as follows: heart rate, 78 ± 7 and 78 ± 6 beats/min; SAP, 93 ± 4 and 94 ± 3 mm Hg; MAP, 69 ± 3 and 70 ± 3 mm Hg; and DAP, 55 ± 3 and 57 ± 4 mm Hg, respectively. There was no significant interaction between anesthetic time and treatment for heart rate (P = 0.35), MAP (P = 0.05), or SAP (P = 0.47); however, mean heart rate decreased significantly (P < 0.01) in both treatment groups over time (Figure 1). A significant (P = 0.03) interaction was found between time and treatment for DAP; however, no significant differences were found at any time points between treatments or over time within the same treatment group (Figure 2).

Mechanical ventilation was instituted in 8 dogs in the acepromazine group and in 11 in the trazodone group. Bradycardia was identified in 14 dogs (8 in the acepromazine group and 6 in the trazodone group). However, this was considered a complication in only 3 dogs in each group for which intervention was required. Intraoperative hypotension developed in 11 dogs (6 in the acepromazine group and 5 in the trazodone group) and the incidence of this complication in the 2 groups was not significantly different (P = 1). One dog in the acepromazine group (that did not have an arterial catheter placed) had copious blood loss. No other complications were recorded during anesthesia.

**Figure 2**—Mean ± SD SAP (A), MAP (B), and DAP (C) measured via an arterial catheter placed in a palmar (n = 17) or dorsal pedal (9) artery of 26 dogs in the acepromazine (12; circles) or trazodone (14; squares) groups. Arterial catheter placement was attempted in all dogs approximately 45 minutes after induction of general anesthesia and was unsuccessful in 4. No significant difference over time was found within or between the 2 treatment groups for any of these variables.
Inotropic agents, specifically dopamine (2.5 to 5 μg/kg/min [1.14 to 2.27 μg/lb/min]; n = 2), dobutamine (2.5 to 5 μg/kg/min; 4), or both (5) were administered to treat hypotension during the anesthetic episode. The 11 affected dogs included 9 of 26 patients (4 and 5 in the acepromazine and trazodone groups, respectively) that had invasive blood pressure monitoring. No differences in mean heart rate (P = 0.78), SAP (P = 0.24), MAP (P = 0.60), or DAP (P = 0.96) were found between the 2 groups when data for dogs that received inotropic agents were compared.

Nine dogs (n = 6 and 3 in the acepromazine and trazodone groups, respectively) required intraoperative analgesic treatment. For the acepromazine group, this included 5 dogs undergoing TPLO (including 1 dog that had bilateral surgery) and 1 undergoing TTA; mean ± SD durations of anesthesia and surgery for these dogs were 214 ± 42 and 103 ± 39 minutes, respectively. For the trazodone group, this included 2 dogs undergoing TPLO and 1 having TTA (mean ± SD durations of anesthesia and surgery, 207 ± 18 and 97 ± 31 minutes, respectively). Treatments included inhalation administration of nitrous oxide in oxygen alone (3); hydromorphone as a bolus, alone (1) or with ketamine and nitrous oxide treatment (1); fentanyl alone as a bolus or constant rate infusion (1 each) or as a constant rate infusion with lidocaine and nitrous oxide treatment (1); and constant rate infusion of morphine-lidocaine-ketamine (1). All dogs recovered from anesthesia without complications. One dog had priapism approximately 24 hours after the administration of trazodone.

The post hoc power analysis revealed that to detect a heart rate difference of 10 beats/min, 18 dogs/group were needed. To identify a 15-mm Hg difference in MAP and DAP, 12 and 10 dogs/group, respectively, were needed. To detect a 1.0 mg/kg difference in the dose of propofol needed for induction, 10 dogs/group was sufficient.

Discussion

Results of the present study revealed no significant differences in the cardiovascular effects of premedication that included acepromazine (0.01 to 0.03 mg/kg, IM) versus trazodone (5 mg/kg for patients > 10 kg or 7 mg/kg for those ≤ 10 kg, PO) in otherwise healthy dogs undergoing general anesthesia and orthopedic surgery. There was no significant difference in the mean dose of propofol needed for anesthetic induction, mean isoflurane vaporizer setting during surgery, mean duration of anesthesia, or median surgical time between the treatment groups. The mean heart rates and blood pressure measurements (SAP, MAP, and DAP) for all dogs, and for the subset of dogs that received inotropes for treatment of intraoperative hypotension, also did not differ between the 2 groups.

Little prospective clinical research has been done on the use of trazodone in dogs. Publications describing treatment with trazodone have been primarily limited to anecdotal information provided by veterinary behavior specialists with personal experience regarding its use in a clinical setting and 1 study of postoperative trazodone use in canine patients with orthopedic conditions. Our subjective observation that an increasing number of patients requiring anesthesia for various reasons had recently received trazodone or were receiving the drug for behavioral modification was the impetus for the present study of the clinical cardiovascular implications of preoperative trazodone treatment.

Trazodone, a triazolopyridine derivative of the phenylperazine drug class, is classified as a serotonin receptor antagonist and reuptake inhibitor and an antagonist of 5-HT2A receptors. Antagonism of α1-adrenergic receptors as well as slight α2-adrenergic receptor antagonism have been implicated in the vasodilatory effects of the drug as well as the complication of priapism in men, and may have been the cause of priapism in 1 dog in the present study.

One retrospective case series evaluated the use of trazodone as an adjunctive treatment with other anxiolytic drugs, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, over a 12-year period for treatment of anxiety in 56 dogs. Trazodone was introduced at an initial dosage of half the target dosage over a few days. Initial dosages were approximately 2.5 to 5 mg/kg, PO, every 12 to 24 hours, and target dosages were approximately 5 to 10 mg/kg, PO, every 8 to 24 hours. The initial dosage was increased after ensuring dogs were tolerant to the drug to avoid any potential adverse gastrointestinal effects. Unfavorable effects of trazodone reported in that study included gastrointestinal upset or sedation. Gastrointestinal effects were not noted in any of the study dogs receiving trazodone in the present study; however, the degree of sedation in these patients was evaluated separately as part of another study. The dose for premedication in dogs of the present study was determined on the basis of information in the described retrospective study as well as the clinical experience of the Behavior Service staff at our facility. After the initial planning and preparation for this study, additional pharmacokinetic information was determined for trazodone in dogs. Jay et al determined that 8 mg/kg (3.6 mg/lb), PO, produced acceptable plasma concentrations of drug with few adverse effects (gastrointestinal signs).

Acepromazine was selected as the alternate treatment in this study because of its common use as a premedicant in healthy dogs and because of the ease of pairing it with an injectable opioid prior to orthopedic surgery. Acepromazine is a phenothiazine and is used as a tranquilizing agent to facilitate sedation in dogs. The drug receptor-binding affinity is greatest toward α1-adrenergic receptors as well as 5-HT2 subfamily serotonin receptors. However, it also has moderate affinity for dopamine receptors (D2 > D1). Antagonism of norepinephrine on α1-adrenergic receptors leads to the compaction of vasodilation and
hypotension commonly observed following administration of acepromazine.\textsuperscript{1,3,18} The dopaminergic antagonism of this drug is primarily responsible for its sedative effects.\textsuperscript{18}

A narrow dosage range of acepromazine was used for administration to dogs of the present study, and the doses administered were substantially lower than the labeled dose as well as that in reference texts.\textsuperscript{1,3} Recommended parenteral doses range from 0.05 to 0.2 mg/kg (0.023 to 0.091 mg/lb) in small dogs and from 0.04 to 0.06 mg/kg (0.018 to 0.027 mg/lb) in large dogs.\textsuperscript{1} The dosage range used in the present study has been recommended for acepromazine when paired with an opioid for premedication.\textsuperscript{19,20}

When the cardiovascular effects of trazodone were compared to those of imipramine, another psychotropic agent, the only cardiovascular abnormalities observed in dogs that received trazodone were a slowing of the normal sinus rhythm and a reduction in MAP.\textsuperscript{7,21} In our study, no significant differences were found between the acepromazine and trazodone groups for any cardiovascular variables, although results of post hoc analysis indicated the number of dogs in each group was insufficient to identify a difference of 10 beats/min in heart rate. Acepromazine is reported to cause alterations in heart rate, most commonly a mild, compensatory tachycardia if a patient is also slightly hypotensive, but occasionally bradycardia can develop.\textsuperscript{5,18}

The lack of significant intergroup differences in SAP, MAP, and DAP in the present study could have been partly attributable to dose-dependent cardiovascular depression and concurrent vasodilation caused by inhalation anesthetic agents.\textsuperscript{22} However, no differences were found in the isoflurane vaporizer settings between the 2 groups. Acepromazine is also known to cause decreases in DAP as a result of vasodilation.\textsuperscript{23} This was not appreciated in our study, possibly because of the low dosages of acepromazine used. The inotropic agents used to improve blood pressure in hypotensive patients were also not associated with significant differences in blood pressure or heart rate between treatment groups. Dopamine was the inotrope of choice owing to its stimulation of α\textsubscript{2} and β-adrenergic receptors.\textsuperscript{24} Dobutamine was the alternative and was used if no improvement in blood pressure resulted from dopamine treatment. In most cases, a combination of dopamine and dobutamine was administered to provide the beneficial receptor activity of both drugs.\textsuperscript{24}

The lack of significant differences between acepromazine and trazodone groups in regard to the mean dose of propofol required for anesthetic induction could have been influenced by the amount of morphine (1 mg/kg) administered as part of the premedication. It is possible that this morphine dose caused enough sedation and sparing effect that the differences in propofol requirements were negligible.\textsuperscript{25} It is also possible that slower administration of propofol could have revealed differences between the 2 groups, considering that rapid induction can result in a higher dose to achieve the clinical endpoint. The propofol administration rate in the present study followed the general guidelines for standard of care at our teaching hospital. A slower delivery could have extended the time required to establish a patent airway, with the potential for complications, especially in a teaching setting.

Complications encountered during the study included intraoperative hemorrhage in 1 dog during TPLO. This dog did not have an arterial catheter in place and therefore was not included in analysis of SAP, MAP or DAP. The dog that developed priapism 24 hours after surgery was retained in the analysis, as this would not have impacted intraoperative cardiovascular variables.\textsuperscript{5}

This study was performed in a clinical setting at a university teaching hospital, which provided some limitations, including the involvement of several different anesthetists and surgeons. Ideally, only 1 anesthetist and 1 orthopedic surgeon would have managed all of the cases for consistency.

Another limitation was the need for additional analgesia for 9 of 30 (30%) patients during the intraoperative period, which could not be compared statistically between the study treatment groups. To suppress nociception and changes in cardiovascular status related to nociception, treatments were given to blunt these sympathetic responses. Of the 30 study dogs, 3 (10%) received a constant rate infusion of a narcotic agent with or without lidocaine, 3 (10%) received a single bolus of a narcotic, and 5 (17%) received supplementary nitrous oxide treatment, alone or in combination with other treatments. Epidural administration of morphine and bupivacaine had been performed prior to surgery in 29 of 30 study dogs; 1 dog did not have this treatment because of superficial dermatitis over the lumbar region. One dog received intraoperative analgesics in response to sympathetic stimulation resulting from substantial blood loss.\textsuperscript{26} The remaining 7 of 30 (23%) dogs likely had epidural analgesic failure. This percentage was much higher than the 4 of 41 (10%) previously reported.\textsuperscript{27} This finding was attributed to the fact that 4th-year veterinary students administered many of the epidural injections, although they were directly supervised by board-certified anesthesiologists. Selection of a less invasive surgical procedure that did not require epidural analgesic administration would have eliminated this variable and the possible confounding of results related to its failure in some patients.

Sympathetic blockade and hypotension can also occur as sequelae to epidural injections.\textsuperscript{27,28} Minimal cardiovascular changes were detected when acepromazine-sedated dogs were given bupivacaine or ropivacaine via epidural injections.\textsuperscript{29} Results of a study\textsuperscript{30} evaluating the motor blockade effects of bupivacaine and levobupivacaine injected epidurally in dogs revealed that at a low concentration (0.25%), complete motor blockade did not develop. Decreases in heart rate or blood pressure were not observed be-
between epidural injection and the start of surgery in any of the dogs of the present study. It is possible that the dose of bupivacaine (0.5 mg/kg) and the concentration of the drug (0.25%) decreased the likelihood of its causing substantial vasodilation and sympathetic ganglionic blockade in the dogs.

Finally, to correctly assess the effect of inhalation anesthetics on the variables of interest, the fraction of expired anesthetic should have been considered in the analysis. Unfortunately, this variable was not available for all dogs, and the vaporizer percentage setting for inhalation anesthetic delivered was used instead. The vaporizers were all precision vaporizers and were routinely calibrated 2 times/y. Furthermore, the dogs enrolled in the study were systemically healthy; therefore, it is reasonable to assume that the anesthetic uptake from the alveoli by the blood was similar in these animals, resulting in comparable fractions of expired anesthetic gases. Only 2 dogs (both in the acepromazine group) received sevoflurane and they were excluded from this part of the analysis. Comparison of the concentrations of sevoflurane and sevoflurane delivered to the dogs in the present study with their corresponding MAC values suggests that the animals received approximately 1.5 X the MAC for each anesthetic. This suggests that the amount of the gases delivered was equipotent and, because sevoflurane and sevoflurane have comparable cardiovascular effects, it is likely that the animals in both groups had similar cardiovascular effects caused by the volatile agents. Any potential MAC-sparing effects of trazodone were not evaluated in this study.

On the basis of our results, we concluded that trazodone can be administered to healthy dogs at the dosages used in this study as part of a preoperative medication protocol in combination with an opioid. In this population of dogs, preoperative treatment with trazodone did not cause any greater impact on cardiovascular variables than did acepromazine. In our hospital, trazodone is also used clinically to premedicate dogs in combination with additional opioid agents.

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Footnotes

b. Morphine sulfate injection, West-Ward Pharmaceuticals, Eatontown, NJ.
d. PropoFlo, Abbott Laboratories, North Chicago, Ill.
e. IsoFlo, Abbott Laboratories, North Chicago, Ill.
g. Tec-4 Vaporizer, Vetland Medical Sales & Services LLC, Louisville, Ky.
i. Datascope Spectrum, Datascope Corp, Mahwah, NJ.
j. Infumorph PF, West-Ward Pharmaceuticals, Eatontown, NJ.
k. Marcaine, Hospira Inc, Lake Forest, Ill.
l. BD Spinal Needle, BD Medical, Franklin Lakes, NJ.
n. ICU Medical Transpac IV Monitoring kit, San Clemente, Calif.
o. Bair Hugger Warming Unit, Augustine Medical Inc, Eden Prairie, Minn.
p. Dobutamine HCl, Hospira Inc, Lake Forest, Ill.
q. Dopamine HCl, Hospira Inc, Lake Forest, Ill.
r. Glycopyrrolate, West-Ward Pharmaceuticals, Eatontown, NJ.
s. Prism, version 6.0, GraphPad Software Inc, La Jolla, Calif.

References


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From this month’s *AJVR*

Serologic survey for antibodies against three genotypes of bovine parainfluenza 3 virus in unvaccinated ungulates in Alabama

Benjamin W. Newcomer et al

**OBJECTIVE**

To determine serum titers of antibodies against 3 genotypes of bovine parainfluenza 3 virus (BPI3V) in unvaccinated ungulates in Alabama.

**ANIMALS**

62 cattle, goats, and New World camels from 5 distinct herds and 21 captured white-tailed deer.

**PROCEDURES**

Serum samples were obtained from all animals for determination of anti-BPI3V antibody titers, which were measured by virus neutralization assays that used indicator (reference) viruses from each of the 3 BPI3V genotypes (BPI3V-A, BPI3V-B, and BPI3V-C). The reference strains were recent clinical isolates from US cattle. Each sample was assayed in triplicate for each genotype. Animals with a mean antibody titer ≤ 2 for a particular genotype were considered seronegative for that genotype.

**RESULTS**

Animals seropositive for antibodies against BPI3V were identified in 2 of 3 groups of cattle and the group of New World camels. The geometric mean antibody titer against BPI3V-B was significantly greater than that for BPI3V-A and BPI3V-C in all 3 groups. All goats, captive white-tailed deer, and cattle in the third cattle group were seronegative for all 3 genotypes of the virus.

**CONCLUSIONS AND CLINICAL RELEVANCE**

Results indicated that BPI3V-A may no longer be the predominant genotype circulating among ungulates in Alabama. This may be clinically relevant because BPI3V is frequently involved in the pathogenesis of bovine respiratory disease complex, current vaccines contain antigens against BPI3V-A only, and the extent of cross-protection among antibodies against the various BPI3V genotypes is unknown. (*Am J Vet Res* 2017;78:239–243)