Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats

Patrick M. McSweeney, DVM; David D. Martin, DVM, DACVA; Deborah S. Ramsey, DVM; Brett C. McKusick, DVM, PhD

Objective—To evaluate the clinical efficacy of dexmedetomidine as a preanesthetic medication administered prior to anesthetic induction with ketamine or propofol and with or without isoflurane for maintenance of anesthesia.

Design—Randomized, blinded, controlled clinical trial.

Animals—184 client-owned cats.

Procedures—Cats requiring general anesthesia for short or long procedures were assigned to receive 1 of 4 preanesthetic and induction drug combinations (dexmedetomidine and ketamine, placebo [saline (0.9% NaCl) solution] and ketamine, dexmedetomidine and propofol, or placebo and propofol). Cats undergoing long procedures received isoflurane for maintenance of anesthesia.

Results—Administration of dexmedetomidine prior to anesthetic induction with ketamine significantly increased the intubation success rate (57/64 [89%]), compared with the success rate for the placebo (4/37 [11%]); significantly reduced the median induction dose of propofol (≤5.1 mg/kg [2.32 mg/lb]), compared with that for the placebo (≤10.5 mg/kg [4.77 mg/lb]); and significantly reduced the isoflurane concentration (1.5%) required for anesthesia maintenance, compared with that for the placebo (3.0%). Postoperatively, fewer cats receiving dexmedetomidine required rescue analgesia, and cats had lower pain scores for at least 2 hours after surgery, compared with results for cats receiving the placebo. Heart rate was lower during the procedure and respiratory rate and rectal temperature were lower during and after the procedure for cats receiving dexmedetomidine. More cats that received dexmedetomidine had emesis and pale mucous membranes, compared with the number of cats with those signs that received placebo.

Conclusions and Clinical Relevance—Dexmedetomidine as a preanesthetic was efficacious for clinical use in cats requiring general anesthesia. (J Am Vet Med Assoc 2012;240:404–412)

α2-Adrenoceptor agonists are commonly used in feline medicine for their dose-dependent sedative and analgesic effects to facilitate veterinary procedures.1 Dexmedetomidine, the d-enantiomer that possesses all relevant pharmacological activity in racemic medetomidine,2 is the newest and most potent α2-adrenoceptor agonist approved by the FDA and commercially available for use as a sedative and preanesthetic in dogs and cats.

One of the more practical uses for α2-adrenoceptor agonists, such as dexmedetomidine, in feline medicine is as part of a combination protocol used prior to or simultaneously with an anesthetic to enhance sedation, analgesia, muscle relaxation, and general anesthesia. Xylazine-ketamine or medetomidine-ketamine combinations reduce the incidence of tonic-clonic seizure-like activity associated with ketamine administration alone,1 improve muscle relaxation, and provide preemptive and short-term postoperative analgesia in cats.3–7 The medetomidine-ketamine combination results in better muscle relaxation and analgesia in a clinical setting when compared with results for other multidrug protocols such as xylazine-ketamine,4,5 acepromazine-ketamine,5 or acepromazine-thiopentone.6 Because ketamine increases sympathetic tone, ketamine may partially prevent bradycardia, a commonly observed adverse effect in cats following administration of an α2-adrenoceptor agonist.5,8

To our knowledge, only 1 study9 has been performed with cats to evaluate the use of dexmedetomidine in combination with ketamine. In that study,9 the dexmedetomidine-ketamine combination resulted in a significant improvement over dexmedetomidine alone with respect to sedation and muscle relaxation and was accompanied by anesthesia of short to medium dura-
tion. However, surgical procedures were not conducted in that study. In another study involving cats, dexmedetomidine administered prior to anesthesia achieved by the use of propofol-sevoflurane and surgery resulted in significant dose-sparing effects and better recovery, compared with results for control cats receiving saline (0.9% NaCl) solution. Dexmedetomidine also provides significantly better analgesia in cats when administered IM at 40 μg/kg (18 μg/lb) prior to a thermal noxious stimulus.\(^5\)^

The objective of the study reported here was to evaluate the clinical efficacy and safety of dexmedetomidine administered as a preanesthetic agent 10 to 15 minutes prior to anesthetic induction with ketamine or propofol, with or without administration of isoflurane for maintenance of anesthesia in cats. To determine the effects of dexmedetomidine, a saline solution placebo was chosen as the negative control treatment in the study reported here. We hypothesized that preanesthetic administration of dexmedetomidine would result in a significant reduction in the amounts of ketamine, propofol, and isoflurane needed for induction and maintenance of anesthesia as well as improve analgesia in cats recovering from elective surgical procedures.

### Materials and Methods

**Animals**—Healthy client-owned cats of any breed and either sex that were at least 12 weeks old, weighed between 1 and 10 kg (2.2 and 22 lb), and were undergoing an elective surgical procedure requiring general anesthesia at 1 of 5 companion animal veterinary practices in the United States were screened for inclusion in the study. Owner consent was obtained for each cat included in the study. The study was conducted in compliance with good clinical practice and anesthetic monitoring guidance.\(^11\)\(^\text{a}\)\(^\text{b}\) The study protocol was approved by the ethical review board of Pfizer Animal Health.

A cat was included in the study when it met the following criteria: the cat was apparently healthy and had no clinically relevant abnormalities detected on a CBC and serum biochemical analysis, the cat was classified with a physical status of category I or II (in accordance with the anesthetic classification system of the American Society of Anesthesiologists), and the cat had not been allowed access to food for at least 12 hours prior to administration of the preanesthetic.

Cats were excluded from the study if they had a recent history of having been bred; were pregnant or lactating; were grossly obese or emaciated; had signs or a history of systemic disease; had a history of hypersensitivity to \(\alpha\)-adrenoceptor agonists, ketamine, propofol, or volatile anesthetic agents; had been treated with sympathomimetic amines, anticholinergics, tranquilizers, sedatives, or analgesic drugs within 48 hours prior to anesthesia; or could not be intubated because of a concurrent physical abnormality. Cats with > 1 anesthetic episode and surgical procedure were included in the study only once.

**Study design**—The study was designed as a randomized, blinded, placebo-controlled clinical trial with 4 experimental groups stratified on the basis of short (≤ 15 minutes) and long (> 15 minutes) procedures. The 4 combination groups used in the randomization were as follows: dexmedetomidine\(^6\) and ketamine,\(^7\) placebo (ie, saline solution) and ketamine, dexmedetomidine and propofol,\(^8\) or placebo and propofol. Within each veterinary clinic, cats were stratified by long- or short-duration procedures. Within procedure duration, cats were randomly allocated according to a generalized block design, with block determined by the order of enrollment. Also within procedure duration, cats were randomly assigned to receive the placebo or dexmedetomidine in a ratio of 3:5, respectively. That is, of the first 16 cats assigned, all treatment groups were represented in the proper ratio: 6 cats in the placebo group (3 ketamine and 3 propofol) and 10 in the dexmedetomidine group (5 ketamine and 5 propofol). Additional cats were assigned in a similar manner to maintain the ratio of 3:5 for the entire study. A randomization schedule of numbers assigned to cats in the study was prepared separately for short and long procedures for each hospital participating in the study. Investigators were given a list of numbers corresponding to each cat enrolled in the study that informed them only of the randomized induction drug; the treatment drug was never disclosed to the investigators.

**Study procedures**—The doses used for the 4 groups were as follows: dexmedetomidine (40 μg/kg, IM) and ketamine (5 mg/kg [2.3 mg/lb], IM), placebo (saline solution; 0.08 mL/kg [0.036 mL/lb], IM) and ketamine (5 mg/kg, IM), dexmedetomidine (40 μg/kg, IM) and propofol (13.2 mg/kg [6 mg/lb], IV to effect), or placebo (0.08 mL/kg, IM) and propofol (13.2 mg/kg, IV to effect). The dose of dexmedetomidine chosen for this study corresponded to the FDA-approved single-use IM dose for sedation and analgesia in cats. The ketamine dose administered after dexmedetomidine was lower than the FDA-recommended IM dose to allow the evaluation of the dose-sparing effect of dexmedetomidine on ketamine and was consistent with doses\(^6\)^\(^9\)\(^\text{a}\) of ketamine used after the administration of an \(\alpha\)-adrenoceptor agonist.\(^2\)^

The veterinarians and all study personnel were not aware of the preanesthetic treatment but were aware of the induction drug throughout the study. The dexmedetomidine and placebo were provided to the veterinarians in identically packaged 10-mL vials and labeled with a number corresponding to a number assigned to each cat that was enrolled via the randomization procedures. Commercially available ketamine and propofol were supplied to the veterinarians in single-use vials (ie, 1 vial/cat).

Signalment (age, sex, breed, color pattern, and demeanor score) for each cat was recorded, and a physical examination was performed ≤ 4 days prior to administration of the preanesthetic. Blood samples were collected for preanesthetic screening, which included a CBC and serum biochemical analysis. On the day of the procedure, the assigned preanesthetic (dexmedetomidine or placebo) was administered to each cat in the cranial aspect of a thigh muscle. Cats were allowed to rest quietly for 10 to 15 minutes, and then each cat was administered the induction drug (ketamine was injected into the cranial aspect of the contralateral thigh muscle, and propofol was injected IV).
Endotracheal intubation was performed by the veterinarian or veterinary technician typically responsible for anesthesia induction at each study site. A laryngoscope could be used to enhance the ability to visually identify the vocal cords during intubation, but lidocaine could not be applied topicaly to the larynx to facilitate intubation. Approximately 5 to 10 minutes after IM administration of ketamine, the veterinarian or veterinary technician determined whether the cat was adequately sedated for intubation. Cats that could not be intubated following ketamine administration were recorded as intubation failures. These cats were then administered isoflurane by use of a face mask until they could be intubated.

For cats receiving propofol for induction of anesthesia, a veterinarian administered propofol to effect by IV injection during a period of 60 to 90 seconds while assessing the cat's degree of sedation and relaxation. If the cat appeared sufficiently sedated, administration of propofol was stopped and intubation was attempted. If intubation was unsuccessful, additional propofol was administered (up to the maximum volume in the syringe). The final volume of propofol injected for induction of anesthesia was recorded. Cats that could not be intubated after administration of propofol were recorded as intubation failures and administered isoflurane by use of a face mask until they could be intubated.

Following endotracheal intubation, the scheduled surgical procedure was performed. Approximately half of the cats enrolled at each study site underwent a procedure of short duration (≤ 15 minutes) during which inhalation anesthesia was not needed. The other half of the cats enrolled underwent a procedure of longer duration (> 15 minutes) during which isoflurane was administered to maintain anesthesia. Duration of the procedure was determined on a case-by-case basis by personnel at each study site. Cats undergoing short-duration procedures received oxygen through the endotracheal tube. Cats undergoing long-duration procedures received oxygen and isoflurane via the endotracheal tube at an oxygen flow rate and vaporizer setting appropriate for the delivery system used (semiclosed or nonrebreathing) and necessary to maintain a surgical plane of anesthesia. Once intubated, the administration of oxygen and isoflurane was recorded as concomitant medications. The vaporizer settings and oxygen flow rates were recorded only after a cat was intubated and not during administration via face mask. External heat sources were used during and after the procedures to help maintain the body temperature of each cat. Following completion of the procedure, the interval until the cat was able to stand was recorded. Water was offered to all cats 4 hours after completion of the procedure. Cats were hospitalized overnight and discharged to the owners the following day. Owners were contacted via telephone by hospital staff 2 to 5 days after the cats were discharged and asked to provide an update on the condition of each cat.

Clinical assessments—All assessments were performed by the same veterinarian or veterinary technician who was responsible for the induction and maintenance of anesthesia in a specific cat. For each cat, assessments of body posture, response to noise, jaw tone, signs of pain, rectal temperature, heart rate and rhythm, and respiratory rate were conducted 5 minutes prior to pre-anesthetic administration (baseline), 10 to 15 minutes after preanesthetic administration, at the start of the procedure, at 15-minute intervals during the procedure, at the end of the procedure, at 30-minute responses for the first 2 hours after the procedure, at 2 and 4 hours after the procedure, and at the time of discharge from the veterinary hospital.

The response of each cat to injection of the pre-anesthetic was subjectively evaluated as none, slight, moderate, or strong. Response to ketamine injection was not evaluated. Sedation was subjectively assessed by use of a method described elsewhere and calculated by summing categorical scores (0 = no effect; 3 = maximum effect) for the cat's posture, response to noise, and muscle tone of the jaw and tongue. Signs of pain were subjectively assessed with a visual analogue scale. A mark corresponding to the perceived pain of each cat was made on a 10 cm line, with 0 at the left end of the line was measured in millimeters (0 mm = no pain; 100 mm = worst possible pain). Respiratory rate was obtained by counting the visually observed chest expansions associated with breathing. Hemoglobin oxygen saturation was assessed with a pulse oximeter (lingual probe) during the procedure. Heart rate and rhythm were assessed by auscultation of the heart or by palpation of an arterial pulse. Heart rhythm was recorded as regular or irregular. Rectal temperature was measured. All assessments were recorded into the medical record of each cat.

Concomitant medications—Any medications administered immediately prior to the procedure, during the procedure, or prior to discharge from the veterinary hospital were recorded. Medications that could have interfered with the evaluation of dexmedetomidine were not administered until 4 hours after completion of the procedure. Prohibited medications included sympathomimetic amines, anticonvulsant drugs, drugs that potentially cause bradycardia, theophylline or amnophylline, and nonprotocol-approved anesthetics, tranquilizers, or sedatives. If a cat had signs of pain at any time during the study, rescue analgesia was administered. The rescue analgesic selected was at the veterinarian's discretion in accordance with the standard perioperative and postoperative analgesia protocols at each respective study site. Any additional analgesics deemed necessary and the time of their administration were recorded as concomitant medications. Analgesics administered ≤ 4 hours after completion of the procedure were considered rescue analgesics. Analgesics administered > 4 hours after completion of the procedure were not considered rescue analgesics.

Adverse events—Adverse events were recorded beginning at the time of preanesthetic administration,
and monitoring continued for 2 to 5 days after discharge from the veterinary hospital. An adverse event was defined as any undesirable event in a cat during the observation period regardless of its relation to the preanesthetic. Adverse events were reported by anyone associated with the study, including the cats’ owners.

Statistical analysis—We hypothesized that preanesthetic administration of dexmedetomidine would result in a significant reduction in the amounts of ketamine, propofol, and isoflurane needed for induction and maintenance of anesthesia and would improve analgesia in cats recovering from elective surgical procedures. Each hospital was to enroll a minimum of 16 cats for both short and long procedures, with the expectation that sufficient information would be obtained from at least 12 cats in each group for statistical analysis. This ensured that no individual hospital contributed > 30% of the data to the analysis. All 5 hospitals were able to enroll and submit data from an adequate number of cats for statistical analyses.

Data for heart rate, respiratory rate, hemoglobin oxygen saturation, body temperature, reaction to injection, and recovery time were summarized for each group (ie, premedication and induction drug combination) by use of descriptive statistics (mean ± SD) only. All statistical analyses were performed with commercially available software.4 Significance was set at a value of P ≤ 0.05. Treatment was defined as dexmedetomidine or placebo. The fixed and random effects included in each model were determined a priori by biostatisticians. Regardless of the outcome of interest, data were analyzed by strata (ie, short and long procedures) that were defined a priori during the design of the study.

To test the effect of dexmedetomidine on ketamine, a generalized linear mixed model was used with a logit link. The outcome variable of interest was intubation success or failure. The fixed effect was treatment. Random effects were hospital and the hospital-by-treatment interaction.

The effect of dexmedetomidine on the amount of propofol needed for induction of anesthesia was analyzed with a mixed linear model. The fixed effect was treatment. Random effects included hospital and the hospital-by-treatment interaction.

A mixed linear model was used to evaluate the effect of dexmedetomidine on the concentration of isoflurane required for maintenance of anesthesia for the duration of long procedures. Fixed effects included treatment, induction drug, and the treatment-by-induction drug interaction. Random effects included hospital and the hospital-by-treatment interaction. If there was a significant effect for the treatment-by-induction drug interaction, then comparisons between treatments were made for each induction drug separately. If there was not a significant effect of the treatment-by-induction drug interaction, then treatments for each induction drug were combined for comparisons.

The effect of dexmedetomidine on the need for rescue analgesia was analyzed by use of a generalized linear mixed model with a logit link. Fixed effects included treatment, induction drug, and the treatment-by-induction drug interaction. The model included the random effects of hospital and the hospital-by-treatment interaction.

The pain visual analogue score was analyzed by use of a mixed linear model for repeated measures. Fixed effects included treatment, induction drug, time, and all possible 2- and 3-way interactions. Random effects included hospital, the hospital-by-treatment interaction, and between and within animal errors. If there was a significant effect for the treatment-by-induction drug interaction or treatment-by-induction drug-by-time interaction, then comparisons between treatments were made for each induction drug at each time. If there was not a significant effect for the treatment-by-induction drug interaction or the treatment-by-induction drug-by-time interaction, then treatments for each induction drug were combined for comparison at each time. Within a treatment, comparisons were also made between values at each time point and baseline values. Long and short procedures were analyzed separately.

Data from long and short procedures were pooled. A Cochran-Mantel-Haenszel test was used to calculate the relative risk and 95% CI for the comparison of intubation success and the need for rescue analgesia while controlling for the procedure duration and induction drug.

Results

Animals—A total of 184 cats (116 dexmedetomidine-treated cats and 68 placebo-treated cats) with a mean ± SD weight of 3.5 ± 1.5 kg (7.7 ± 3.3 lb [range, 0.9 to 8.2 kg (2.0 to 18.0 lb)]) and mean ± SD age of 2.2 ± 3.2 years (range, 0.2 to 16 years) were enrolled in the study. Female cats (101 [55%]) outnumbered male cats (83 [45%]), and most cats (134 [73%]) were domestic shorthair.

The most frequently performed short procedures (n = 90 cats) were orchietomy (53 [59%]), onychectomy (22 [24%]), and ovariohysterectomy (12 [13%]). Dental cleaning, debridement, biopsies, and nodule removal were also performed in the short procedure group. The most frequently performed long procedures (n = 93 cats) were ovariohysterectomy (50 [54%]), dental cleaning (17 [18%]), and onychectomy (15 [16%]). Mastectomy, abdominal wall surgery, entropion repair, tumor removal, orchietomy, and amputation were also performed on cats in the long procedure group. Surgery was not performed on 1 cat in the dexmedetomidine-propofol group because a scar from a previous ovariohysterectomy was detected on the cat during surgical preparation. This cat was not included in the analyses of efficacy (n = 183 cats; Table 1), but was included in the summaries on adverse events (184; Table 2).

Two placebo-treated cats in which anesthesia was induced with ketamine could not be intubated and were considered intubation failures. In both cats, lidocaine was applied topically to the larynx to facilitate intubation. One cat in the placebo-ketamine group was reintubated shortly thereafter when fluid was noticed in the endotracheal tube. That cat was not reintubated for the procedure.

Effects of dexmedetomidine—When ketamine was used for induction of anesthesia, intubation suc-
success rate was significantly higher in cats preanesthetized with dexmedetomidine (dexmedetomidine-ketamine, 27/30 [90%] and 30/34 [88%]) for short and long procedures, respectively), compared with the success rate for placebo-treated cats (placebo-ketamine, 1/18 [6%] and 3/19 [16%] for short and long procedures, respectively; Table 1). Intubation success rate was higher (but not significantly so) in propofol-induced cats preanesthetized with dexmedetomidine (dexmedetomidine-propofol, 26/27 [96%] and 24/24 [100%] for short and long procedures, respectively), compared with the success rate for placebo-treated cats (placebo-propofol, 12/15 [80%] and 14/16 [88%] for short and long procedures, respectively). Regardless of the procedure duration, dexmedetomidine-treated cats were 2.1 times (95% CI, 1.6 to 2.8) as likely to be successfully intubated as were placebo-treated cats. Dexmedetomidine significantly reduced the median induction dose of propofol (≤ 5.1 mg/kg [2.3 mg/lb]) necessary for intubation, compared with the dose of propofol (≥ 10.5 mg/kg [4.8 mg/lb]) for cats administered the placebo preanesthetic. Dexmedetomidine administered as a preanesthetic significantly reduced the median concentration of isoflurane (1.5%; 95% CI, 1.3% to 1.8%) required for maintenance of anesthesia, compared with the concentration of isoflurane (3.0%; 95% CI, 2.6% to 3.2%) required for cats that received the placebo prior to a long procedure. Fewer cats in the dexmedetomidine groups (dexmedetomidine-ketamine, 7/30 [23%] and 3/34 [15%]; dexmedetomidine-propofol, 4/27 [15%] and 4/24 [17%]; Table 1) required rescue analgesia following short or long procedures, compared with the number of cats requiring rescue analgesia in the placebo groups (placebo-ketamine, 11/18 [61%] and 11/19 [58%]; placebo-propofol, 7/15 [47%] and 8/16 [50%]). When controlling for the procedure duration and induction drug, placebo-treated cats were 3.1 times (95% CI, 2.0 to 4.0) as likely to require rescue analgesia, compared with dexmedetomidine-treated cats. When pain was assessed with the visual analogue scale, cats receiving the preanesthetic placebo had significantly higher scores than did cats receiving dexmedetomidine during the 4-hour postoperative observation period (Figure 1). For the first 4 hours after the procedure, the mean pain score for dexmedetomidine-treated cats did not differ significantly from the baseline score. The time to recovery from anesthesia (time to standing) was shortest (mean ± SD, 27 ± 18 minutes) for cats in the dexmedetomidine-ketamine group, intermediate (31 ± 17 minutes) for cats in which anesthesia was induced with propofol (regardless of premedication), and longest (38 ± 15 minutes) for cats in the placebo-ketamine group.

**Adverse events** — The distribution of reactions to preanesthetic injection (ie, none, mild, moderate, or severe) was similar between treatments; 45 of 116 (39%) and 31 of 68 (46%) cats in the dexmedetomidine and placebo groups, respectively, had no reaction to injection. Only a small number of cats had a strong reaction or vocalization to the preanesthetic injection (8 [7%] and 3 [4%] for the dexmedetomidine and placebo groups, respectively).

---

### Table 1—Successful endotracheal intubation and the requirement for rescue analgesia after preanesthetic administration of dexmedetomidine (DEX) or a placebo (PLB; saline [0.9% NaCl] solution) and subsequent induction of anesthesia with ketamine or propofol in healthy cats undergoing elective surgical procedures.

<table>
<thead>
<tr>
<th>Procedure group*</th>
<th>Induction drug</th>
<th>Preanesthetic treatment</th>
<th>No. of cats</th>
<th>No. (%) successfully intubated</th>
<th>Median (range) anesthetic induction dosage (mg/kg)</th>
<th>No. (%) of cats receiving rescue analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short</td>
<td>Ketamine</td>
<td>DEX</td>
<td>20</td>
<td>27 (90)*</td>
<td>5</td>
<td>7 (23)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PLB</td>
<td>18</td>
<td>1 (6)*</td>
<td>5</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Long</td>
<td>Ketamine</td>
<td>DEX</td>
<td>34</td>
<td>30 (88)*</td>
<td>5</td>
<td>11 (58)*</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
<td>DEX</td>
<td>19</td>
<td>3 (16)*</td>
<td>5</td>
<td>11 (58)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PLB</td>
<td>16</td>
<td>14 (88)</td>
<td>5</td>
<td>5 (15)*</td>
</tr>
</tbody>
</table>

* Short procedures were ≤ 15 minutes in duration, and long procedures were > 15 minutes in duration.

**Within an induction drug and within a procedure group, values with different superscript letters differ significantly (P < 0.05).**

---

### Table 2—Number of adverse events observed in cats preanesthetized with dexmedetomidine or a placebo (saline solution) and in which anesthesia was induced with ketamine or propofol.

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of cats at risk</th>
<th>(Ketamine)</th>
<th>(Propofol)</th>
<th>(Ketamine)</th>
<th>(Propofol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emiss or retching</td>
<td>21</td>
<td>21</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pale mucus membranes</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in rectal temperature</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loose feces</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Apnea</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Signs of pain in paws</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Behavioral change</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Corneal injury</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fluid in endotracheal tube</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**Unauthenticated | Downloaded 01/27/24 02:30 AM UTC**
Mean heart rate was lower for cats preanesthetized with dexmedetomidine (115 beats/min), compared with the mean heart rate for cats receiving the placebo (160 beats/min) during the procedure (Figure 2). Heart rate in dexmedetomidine-treated cats began to return to baseline values by 4 hours after the procedure. Cats in which anesthesia was induced with ketamine had a mean heart rate during the procedure that was higher than, but not significantly different from, the mean heart rate in cats in which anesthesia was induced with propofol. Bradycardias (sinus pause and first- and second-degree atrioventricular block) were occasionally observed and detected only in cats preanesthetized with dexmedetomidine (17/64 [27%] and 20/92 [38%] cats in which anesthesia was induced with ketamine and propofol, respectively), compared with results for cats preanesthetized with the placebo. Complete atrioventricular block was not observed in any cat. Tachyarrhythmias (supraventricular and ventricular premature depolarization) were rarely detected (2/116 [2%] dexmedetomidine-treated cats; both cats had anesthesia induced with ketamine).

Compared with baseline values, mean respiratory rate was similarly decreased for all groups during the procedure. Cats in which anesthesia was induced with ketamine had a mean respiratory rate during the procedure that was higher than, but not significantly different from, the mean respiratory rate in cats in which anesthesia was induced with propofol. Respiration in ketamine-treated cats began to return to baseline values by 1 hour after the procedure. Cats in which anesthesia was induced with propofol had a mean respiratory rate during the procedure that was lower than, but not significantly different from, the mean respiratory rate in cats in which anesthesia was induced with ketamine. Respiration in propofol-treated cats began to return to baseline values by 3 hours after the procedure.

Rectal temperature was similarly decreased for all groups during the procedure. Cats in which anesthesia was induced with ketamine had a mean rectal temperature during the procedure that was lower than, but not significantly different from, the mean rectal temperature in cats in which anesthesia was induced with propofol. Rectal temperature in ketamine-treated cats began to return to baseline values by 1 hour after the procedure. Cats in which anesthesia was induced with propofol had a mean rectal temperature during the procedure that was lower than, but not significantly different from, the mean rectal temperature in cats in which anesthesia was induced with ketamine. Rectal temperature in propofol-treated cats began to return to baseline values by 3 hours after the procedure.

Figure 1—Least squares mean ± SE scores for a visual analogue scale (0 to 100 mm) of postoperative pain in cats undergoing a short (<15 minutes; A) or long (>15 minutes; B) surgical procedure. Cats were preanesthetized with dexmedetomidine or a placebo (saline [0.9% NaCl] solution), and anesthesia was induced with ketamine or propofol. The 4 groups were dexmedetomidine-ketamine (black squares), dexmedetomidine-propofol (white squares), placebo-ketamine (black circles), and placebo-propofol (white circles). For cats undergoing long procedures, anesthesia was maintained with isoflurane (B). Time 0 corresponds to the end of the procedure. In panel B, the treatment-by-induction drug statistical interaction was not significant; therefore, treatment means are summarized for each preanesthetic (ie, dexmedetomidine [black triangles] and placebo [white triangles]). Pain score was determined by placing a mark corresponding to the perceived pain of each cat on a 10-cm line and measuring the distance from the left end of the line to the mark in millimeters (0 mm = no signs of pain; 100 mm = signs of worst possible pain). *Within a group, value differs significantly (P ≤ 0.05) from the value at time 0.

Figure 2—Mean ± SD heart rate (A), respiratory rate (B), and rectal temperature (C) in cats preanesthetized with dexmedetomidine or a placebo and in which anesthesia was induced with ketamine or propofol and maintained with (long procedures) or without (short procedures) isoflurane. Data from short and long procedures have been pooled. To convert temperature from Celsius to Fahrenheit, multiply value by 9/5 and add 32 to the product. See Figure 1 for remainder of key.
procedure. Respiratory rate returned more slowly to baseline values in dexmedetomidine-treated cats, compared with that in placebo-treated cats. Hemoglobin oxygen saturation ranged between 90% and 99% (median, 97% for all groups) during the procedure and was not significantly different between treatments.

Rectal temperature decreased in all groups from baseline to the end of the procedure. The rectal temperature of cats treated with dexmedetomidine continued to decrease (to approx 36.4°C [97.5°F]) for the first 2 hours during recovery before starting to return to the reference range by 4 hours after surgery. Rectal temperatures in cats given the placebo typically returned to baseline values by 2 hours after the procedure.

The most frequently observed adverse events were emesis or retching, pale mucous membranes, and decreased rectal temperature (Table 2). These events were observed more frequently in dexmedetomidine-treated cats than in placebo-treated cats. All adverse events were observed by veterinarians or veterinary staff, and no adverse events were reported by owners during the 2- to 5-day postdischarge observational period.

Other medications—The medications most commonly administered concomitantly with dexmedetomidine were the long-acting analesgesics meloxicam and buprenorphine; they were used for pain management during hospitalization and at home. Consistent with routine feline practice, a variety of vaccines (eg, rabies, FeLV, and feline viral rhinotracheitis), antiparasitics (eg, nitrofurazone, pyrantel, selamectin, pyrethrin, praziquantel, fenbendazole, ivermectin, and fipronil), and antimicrobials (eg, penicillin, nitrofurazone, cevofecin, amoxicillin, and clindamycin) were administered during or after the procedures performed in the study. No adverse reactions associated with the use of these products after dexmedetomidine administration were recorded. The distribution of concomitant medications was similar for cats treated with dexmedetomidine or the placebo.

Discussion

The clinical trial reported here revealed a reduction in the amount of ketamine and propofol required for inducing and the concentration of isoflurane required for maintaining a surgical plane of anesthesia in cats following the administration of dexmedetomidine as a preanesthetic. These results confirm findings from previous studies on the usefulness of α₂-adrenoceptor agonists as preanesthetics. The dose of ketamine (5 mg/kg) used for anesthetic induction in the present study was 77% to 85% less than the current FDA-approved dose and resulted in successful intubation of 57 of 64 (89%) cats. Similar to results of another study, cats preanesthetized with dexmedetomidine required 58% less propofol to achieve intubation and required 50% less isoflurane during the surgical procedure to maintain adequate anesthesia, compared with the amounts required for cats preanesthetized with a saline solution placebo. Veterinarians must be cognizant of the dose-sparing effects of dexmedetomidine on other sedatives and anesthetics to avoid overanesthetizing veterinary patients.

The results of the study reported here corroborate other reported clinical benefits of α₂-adrenoceptor agonist preanesthetics. Dexmedetomidine or medetomidine administered as a preanesthetic facilitates the handling of veterinary patients during induction of anesthesia because of their anxiolytic and stress-reducing properties. When xylazine, medetomidine, or dexmedetomidine is administered prior to or concurrently with ketamine, muscle relaxation, hypnosis, and analgesia are enhanced. In contrast, the administration of ketamine alone has been associated with tonic-clonic rigidity during anesthesia accompanied by poor recovery in cats. In the present study, the ketamine-induced rigidity, excitability, and poor recovery commonly observed in cats administered ketamine alone were not observed, most likely because of the low dose of ketamine used.

Reduction in perioperative stress and improvements in analgesia as a result of administration of dexmedetomidine or medetomidine as preanesthetics is attributable to a smooth recovery from anesthesia. In addition to its sedative properties, the dose-dependent analgesic effects of dexmedetomidine have been reported. With recent advancements in the recognition and prevention of pain in veterinary patients, preemptive multimodal analgesia protocols that target pain pathways from different yet possibly synergistic mechanisms have attracted substantial attention from veterinarians.

In the study reported here, cats receiving a placebo as a preanesthetic and in which anesthesia was induced with ketamine appeared to have more signs of pain than did cats in which anesthesia was induced with propofol. This was unexpected because propofol provides no analgesia, and ketamine has only weak visceral analgesic effects. It is possible that ketamine caused the difficult recoveries observed in cats in the ketamine-placebo group and confounded the pain scoring. In contrast, cats preanesthetized with dexmedetomidine had less pain as determined on the basis of their visual analogue scores, compared with scores for cats preanesthetized with the placebo, regardless of the anesthetic induction drug administered. The use of a dexmedetomidine-ketamine or medetomidine-ketamine combination offers perioperative analgesia superior to that of other commonly used drug combinations such as xylazine-ketamine, acepromazine-ketamine, or acepromazine-thiopental in feline medicine. Veterinarians should also be aware that the duration of clinical analgesia provided by dexmedetomidine was only 2 to 4 hours; therefore, additional postoperative analgesics should be considered on the basis of procedure type and observed severity of pain.

Some veterinarians have been hesitant to adopt a sedative or anesthetic protocol that includes dexmedetomidine. Reluctance to use dexmedetomidine might be because α₂-adrenoceptor agonists cause peripheral vasoconstriction that leads to a compensatory reduction in heart rate. Ketamine has sympathomimetic properties and as such should counteract the bradycardic effects of α₂-adrenoceptor agonists. As evidence of this, heart rates in the present study at most of the clinical assessment points were higher (but not significantly so) for cats preanesthetized with dexmedetomidine and in which anesthesia was induced with...
ketamine, compared with heart rates for cats preanesthetized with dexmedetomidine and in which anesthesia was induced with propofol. Also, the mean heart rate reported for cats receiving a dexmedetomidine-ketamine combination was higher in this study than that reported in another clinical trial in which cats were given the same dose of dexmedetomidine (40 µg/kg, IM) but did not receive ketamine. In another study, heart rates in cats that received dexmedetomidine (10 µg/kg [4.5 mg/lb], IM) were lower than, but not significantly different from, heart rates in cats that received dexmedetomidine (10 µg/kg, IM) and ketamine (5 mg/kg, IM). Thus, dexmedetomidine-ketamine combinations provide complementary physiologic effects that are possibly more advantageous than administration of each agent alone; dexmedetomidine provides muscle relaxation and analgesia, whereas ketamine helps mitigate bradycardia.

Cardiac arrhythmias have been reported following α2-adrenoceptor agonist administration and are an expected effect associated with the reduction in heart rate and cardiac conduction velocity. In the present study, sinus bradycardia and sinus arrhythmias were frequently observed in dexmedetomidine-treated cats; however, none of these resulted in adverse clinical reactions. Veterinarians with experience administering α2-adrenoceptor agonists are aware and attentive to the possibility of compromised cardiovascular function. Generally, abnormal cardiac function does not persist for prolonged periods and does not require clinical intervention. Nonetheless, veterinarians may be tempted to prevent or treat dexmedetomidine-induced bradycardia with anticholinergics. The investigators in the present study did not use anticholinergics in any cat, which is consistent with recommendations from studies in which investigators report adverse consequences (eg, hypertension and increased myocardial oxygen consumption) with the use of anticholinergics prior to or in combination with dexmedetomidine in cats and dogs.

A reduced respiratory rate was observed in all groups during anesthesia in the present study, but was not accompanied by clinically important changes in oxygen saturation of hemoglobin. However, the authors acknowledge that it is unknown whether these cats were ventilating adequately because the end-tidal partial pressure of CO2 or Paco2 was not measured. The most profound respiratory decrease was detected shortly after ketamine administration in both groups. Apnea was reported as an adverse event in 1 cat in the dexmedetomidine-ketamine group, but the cat recovered uneventfully. Profound respiratory depression is not characteristic after administration of medetomidine or dexmedetomidine, but ketamine is capable of inducing a transient dose-dependent apnea. Indeed, in another study, a lower mean respiratory rate was reported for cats treated with dexmedetomidine-ketamine (range, 17 to 30 breaths/min), compared with the rate in cats treated with dexmedetomidine alone (range, 30 to 43 breaths/min). Results of studies on dexmedetomidine-ketamine combinations have similarly indicated decreased respiratory rates in cats. However, the incidence of apnea in cats was higher after administration of xylazine-ketamine than after administration of medetomidine-ketamine. In clinical practice, the incidence of apnea may be caused by a dose of ketamine that is too high (> 5 mg/kg), relative to the dose of the α2-adrenoceptor agonist. The low incidence of apnea observed in the study reported here suggests the doses of dexmedetomidine and ketamine were clinically appropriate. The importance of having oxygen and ventilatory support available when dexmedetomidine-ketamine combinations are used for anesthesia of cats should not be ignored. Propofol is also reported to cause respiratory depression; however, this happened infrequently in the present study, presumably because less propofol was used in the dexmedetomidine-treated cats.

The overall incidence of adverse events reported in the present study was relatively low. The most commonly reported adverse event was emesis or retching, which is associated with central stimulation of the area postrema by α2-adrenoergic agonists. Although no firm evidence exists on the relationship between withholding food and the incidence of vomiting in cats administered α2-adrenergic agonists, veterinarians in the present study instructed owners to withhold food from cats for 12 hours prior to anesthesia. The frequent occurrence of vomiting substantiates the recommendation that veterinarians should be prepared to maintain patent airways and prevent aspiration of vomitus following administration of an α2-adrenoceptor agonist.

Peripheral vasoconstriction was manifested as pale mucous membranes in 20 of 115 (17%) dexmedetomidine-treated cats in the present study. Although hypothermia was reported in only a few cats, rectal temperature typically decreases during sedation and anesthesia because of reduced muscular activity, muscle relaxation, and direct adrenergic agonist effects on thermoregulation. As a result, thermoregulation must be addressed following dexmedetomidine administration, especially during the recovery period.

In the study reported here, we detected a marked dose-sparing effect of dexmedetomidine on dosages of ketamine and propofol required for intubation and isoflurane required for maintenance of anesthesia in healthy cats. Emesis, hypothermia, apnea, and cardiac arrhythmia were observed in some cats, which emphasized the necessity for close monitoring of patients during and after procedures. Dexmedetomidine administered as a preanesthetic was found to be efficacious for clinical use in cats undergoing surgical procedures.

References
5. Versteegen J, Forgetton X, Donnay J, et al. An evaluation of me- detomidine/ketamine and other drug combinations for anaes-
8. Selmi AL, Mendes GM, Lins BT, et al. Evaluation of the sedative and cardiorespiratory effects of dexmedetomidine, dexmedeto-
9. Mendes GM, Selmi AL, Barbudo-Selmi GR, et al. Clinical use of dexmedetomidine as premedicant in cats undergoing propofol-
10. Slingsby LS, Taylor PM. Thermal antinociception after dexme-
14. Brodbelt DC, Pfeiffer DU, Young LE, et al. Results of the confi-
dential enquiry into perioperative small animal fatalities regard-
15. Benson GJ, Grubb TL, Neff-Davis C, et al. Perioperative stress response in the dog: effect of pre-emptive administration of me-
16. Ko JC, Mandsager RE, Lange DN, et al. Cardiorespiratory re-
17. Vaisanen M, Raekallio M, Kuusela E, et al. Evaluation of the peri-
operative stress response in dogs administered medetomidine or acepromazine as part of the preanesthetic medication (Erratum pub-
18. Ansah OB, Raekallio M, Vainio O. Comparison of three doses of dexmedetomidine with medetomidine in cats following intra-
20. Pertovaara A, Kauppila T, Jyväsjärvi E, et al. Involvement of sup-
21. Murrell JC, Hellebrekers LJ. Medetomidine and dexmedeto-
23. Schmeling WT, Kampine JP, Roerg D, et al. The effects of the stereoisomers of the α₂-adrenergic agonist medetomidine on systemic and coronary hemodynamics in conscious dogs. Anes-
24. Kuusela E, Raekallio MR, Hetanen H, et al. 24-hour Holter monitor-
25. Vaisanen MAM, Vainio OM, Raekallio MR, et al. Results of 24-
hour ambulatory electrocardiography in dogs undergoing ovar-
27. Alvaides RK, Teixeira Neto FJ, Aguiar AJA, et al. Sedative and cardiorespiratory effects of acepromazine or atropine given be-
28. Dohrmylsky P. Cardiovascular changes associated with anaes-
30. MacDonald E, Scheinin H, Scheinin M. Behavioural and neuro-