Evaluation of dexmedetomidine and ketamine in combination with various opioids as injectable anesthetic combinations for castration in cats

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Objective—To compare the efficacy and cardiorespiratory effects of dexmedetomidine-ketamine in combination with butorphanol, hydromorphone, or buprenorphine with or without reversal by atipamezole in cats undergoing castration.

Design—Prospective, randomized, split-plot, blinded study.

Animals—30 healthy male cats.

Procedures—Cats were assigned to receive dexmedetomidine (25 µg/kg [11.4 µg/lb]) and ketamine (3 mg/kg [1.4 mg/lb]) with butorphanol (0.2 mg/kg [0.09 mg/lb]; DKBut; n = 10), hydromorphone (0.05 mg/kg [0.023 mg/lb]; DKH; 10), or buprenorphine (30 µg/kg [13.6 µg/lb]; DKBup; 10). Drugs were administered as a single IM injection. Supplemental isoflurane was administered to cats if the level of anesthesia was inadequate for surgery. At the conclusion of surgery, half the cats (5 cats in each treatment group) received atipamezole (250 µg/kg [113.6 µg/lb], IM) and the remainder received saline (0.9% NaCl) solution IM. All cats received meloxicam (0.2 mg/kg, SC) immediately prior to the conclusion of surgery.

Results—All drug combinations induced lateral recumbency, and intubation was achievable in 10 of 20 (50%) cats at 10 minutes after injection. Supplemental isoflurane was needed for the surgery in 1 of 10 of the DKBut, 2 of 10 of the DKh, and 7 of 10 of the DKBup-treated cats. Cats that received atipamezole had a significantly shorter recovery time.

Conclusions and Clinical Relevance—DKBut and DKh combinations were suitable injectable anesthetic protocols for castration in cats commencing at 10 minutes after injection, but cats receiving DKBup may require additional time or anesthetics for adequate anesthesia. (J Am Vet Med Assoc 2011;239:1453–1462)

Dexmedetomidine is a synthetic α₂-adrenoreceptor agonist with sedative and analgesic properties.¹ Chemically, dexmedetomidine is a dextrorotary enantiomer of the racemic mixture medetomidine.¹ Studies²,³ have evaluated dexmedetomidine (10 µg/kg [4.35 µg/lb], IV) as a premedication in cats undergoing ovariohysterectomy in which anesthesia was induced with propofol and maintained with sevoflurane and dexmedetomidine at 40 µg/kg (18.18 µg/lb), IM, as the sole sedative agent for various procedures, such as radiography, dental care, grooming, and lancing of abscesses. These studies²,³ concluded that dexmedetomidine administration alone induced adequate sedation and analgesia in cats. When dexmedetomidine (10 µg/kg, IM) administration alone was compared with dexmedetomidine (10 µg/kg) and ketamine (5 mg/kg [2.27 mg/lb], IM) or with dexmedetomidine (10 µg/kg) and butorphanol (0.2 mg/kg [0.09 mg/lb], IM) administration in cats, it was found that the dexmedetomidine-ketamine combinations with ketamine or butorphanol induced more sedation than was achieved with dexmedetomidine administration alone without causing any clinically relevant cardiorespiratory effects.⁴ Various opioids, including butorphanol, hydromorphone, and buprenorphine, have been suggested for use in combination with dexmedetomidine and ketamine in dogs and cats.⁵ A recent study⁶ evaluated the use of dexmedetomidine-ketamine in combination with each of the 3 opioids in dogs undergoing castration. It was concluded that DKBup was the most suitable injectable anesthesia combination.⁶ A review of the literature found no published evaluations of the administration of dexmedetomidine-ketamine with an opioid for short surgical procedures in cats. Because small animal practices commonly use anesthetic protocols with injectable anesthetics, either alone or with

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**Abbreviations**

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DKBut</td>
<td>Dexmedetomidine-ketamine-butorphanol</td>
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<tr>
<td>DKh</td>
<td>Dexmedetomidine-ketamine-hydromorphone</td>
</tr>
<tr>
<td>DKBup</td>
<td>Dexmedetomidine-ketamine-buprenorphine</td>
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<tr>
<td>S°p₀</td>
<td>Saturation of hemoglobin with oxygen as measured by pulse oximetry</td>
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The authors thank Dr. Tomohito Inoue and Jennifer Montgomery for technical assistance.

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inhalant anesthetics for short surgical procedures, it is worthwhile to investigate dexmedetomidine-ketamine–opioid-based anesthetic combinations.

In a dexmedetomidine dose-evaluation study that used a thermal threshold response to test antinociception in cats, an analgesic response was not seen with an injection of dexmedetomidine at 2 to 20 µg/kg (0.9 to 9.1 µg/lb), IM. However, an analgesic response was seen with a higher dose of dexmedetomidine (40 µg/kg, IM). Both doses of dexmedetomidine (20 and 40 µg/kg, IM) induced profound sedation in cats. In a clinical context, it is unknown whether combining a clinical dose of opioids and ketamine with a lower dose of dexmedetomidine (25 µg/kg [11.36 µg/lb], IM) would be sufficient to rapidly induce anesthesia for castration in cats. Furthermore, it is unknown which specific opioid is optimal for use with a dexmedetomidine-ketamine combination in cats undergoing castration. Compared with buprenorphine, butorphanol has a superior and more immediate synergistic effect when used with dexmedetomidine in dogs. This fact was demonstrated in a study comparing IM administration of dexmedetomidine (500 µg/m² [approx. 20 µg/kg for a 20-kg [44-lb] dog]) with either butorphanol (0.2 mg/kg) or buprenorphine (0.015 mg/kg [0.007 mg/ml]) for sedation for joint radiography in dogs. Dexmedetomidine-buprenorphine administration induced a poor quality of sedation, compared with dexmedetomidine-butorphanol administration. Additional buprenorphine administration was necessary to achieve appropriate depth of sedation to begin the procedure. The authors concluded that the use of dexmedetomidine and buprenorphine for profound sedation for radiographic procedures in dogs is not recommended.

It is unknown whether the administration of dexmedetomidine-buprenorphine combined with the more rapid onset action of ketamine would induce a suitable surgical plane of anesthesia for castration in cats in a clinical setting. It is also unknown what effects atipamezole would have on the reversal of these combinations. Atipamezole is a specific antagonist for dexametomidine and has been used to reverse the effects of dexametomidine in cats. In a previous study in dogs undergoing castration, the duration of anesthetic recovery time of dogs that received dexmedetomidine–ketamine-opioid combinations was significantly shortened with atipamezole administration at the conclusion of surgery with minimal adverse effects.

The purposes of the study reported here were to evaluate and compare the anesthetic efficacy and cardiorespiratory effects of dexmedetomidine-ketamine–opioid combinations. All drugs were drawn up separately and mixed in the same syringe immediately prior to administration. All drugs were administered IM in either the right or left quadriceps femoris muscles. An injection of meloxicam (0.2 mg/kg, SC) was administered to each cat immediately prior to the conclusion of surgery. All surgeries were performed by an experienced surgeon (BRA). The surgeon and anesthetists were blinded to the treatment protocols.

**Surgical procedures**—A small incision was made through the scrotum over each testis, and the testis was exteriorized. The spermatic cord was tied onto itself for hemostasis, and the testis was removed. The scrotal incisions were left open to heal by second intention.

**Cardiorespiratory monitoring**—Heart rate, respiratory rate, indirect blood pressure (measured by the same oscillometric device consistently throughout the study), and body temperature were continuously monitored. These recordings started at 5 minutes prior to the drug administration at 0 minutes. Six minutes after drug administration, heart rate and respira-
ory rate were determined by auscultation, SpO2 was determined, noninvasive blood pressure was measured by the oscillometric device, and body temperature was recorded. The same variables were measured and recorded 10 minutes after drug administration and then every 5 minutes thereafter until anesthesia was reversed (approx 20 minutes after drug injection) or the animal recovered spontaneously to sternal recumbency. End-tidal partial pressure of CO2 was measured with a mainstream capnograph if the cat was able to be intubated. An ECG was continuously monitored until surgery was completed. To assess the respiratory effect of the injectable combinations, the cats were maintained on room air. If the SpO2 was < 90% during anesthesia, 100% oxygen was administered until the SpO2 was > 95%.

Monitoring of anesthesia and analgesia—Time from injection of the anesthetics to the onset of sedation, lateral recumbency, and completion of endotracheal intubation were recorded. Ten minutes were allotted from drug administration to complete endotracheal intubation. During these 10 minutes, based on the cat’s clinical signs in response to intubation, 3 attempts were permitted for endotracheal intubation. The ease of endotracheal intubation was scored according to preset criteria (Appendix 1). Once intubated, the endotracheal tube was left in place until the cat began to swallow and cough against the tube. At that time, the endotracheal tube was removed and the total time of intubation was recorded. If the cat could not be intubated, this was recorded and the surgery performed without endotracheal intubation. An additional 10 minutes was allowed for surgical preparation and completion of surgery.

Other recorded variables included the time from injection of anesthetics to the beginning of surgery and the total time of the surgical procedure. To compare anesthesia quality among the injectable anesthetic combinations, every attempt was made to standardize the procedures. The overall quality of anesthesia and recovery were graded according to preset criteria (Appendices 2 and 3).

During the surgery, based on the clinical judgment of the anesthetists or if an animal had signs of inadequate anesthesia such as increased heart rate or respiratory rate or purposeful movements related to surgical stimulation, isoflurane with 100% oxygen was titrated to effect via endotracheal tube or face mask connected to a nonre-breathing anesthetic circuit (modified Jackson-Rees anesthetic circuit) until an adequate plane of anesthesia was achieved. When isoflurane use was required, administration was started at 2% and titrated to effect. When the animal reached a stable plane of anesthesia, the end-tidal isoflurane concentration was recorded from either the endotracheal tube or through the well-fitted face mask and administration of isoflurane was discontinued. If the animal continued to have signs of a light plane of anesthesia, isoflurane supplementation was reinstituted. The total duration of isoflurane supplementation was recorded. The number of cats that received isoflurane supplementation in each group was recorded and compared.

Once castration was completed, either atipamezole or the same volume of saline solution was administered.
IM to the cat according to the treatment group. Time required for cats to achieve sternal recumbency after atipamezole or saline solution administration and time required for cats to maintain standing position after atipamezole or saline solution administration were also recorded. The cat was observed for any signs of pain during recovery. Pain behavior was scored and recorded according to set criteria (Appendix 4). An additional dose of the same opioid was given to cats that had signs of pain during the recovery period (within the first 3 hours after surgery). The number of cats that required an additional dose of an opioid as rescue analgesia was also recorded. Cats were placed on circulating heating blankets during surgery, and forced-air warmers were used during recovery to maintain a body temperature ≥36.7°C (98°F).

**Statistical analysis**—All data were analyzed with a commercially available software program. Analysis of variance procedures were used to determine the significance of the differences attributable to treatment groups. Factorial models were fit and repeated-measures models used when data were considered over time. Effects of treatments with saline solution alone and atipamezole were assessed over time, and when significant, pairwise t tests were performed to further ascertain differences in treatment groups. All data are presented as mean ± SEM. Values of P ≤ 0.05 were considered significant.

**Results**

**Anesthesia quality**—The onset of sedation occurred from 1.2 ± 0.2 minutes to 2.0 ± 0.3 minutes after injection and was followed by a smooth induction of anesthesia. Lateral recumbency occurred from 2.6 ± 0.2 minutes to 4.6 ± 1.0 minutes after the single IM injection for each anesthetic combination. The time from anesthetic administration to the beginning of surgery was from 10.8 ± 1.2 minutes to 14.0 ± 1.8 minutes. The duration of surgery was from 2.8 ± 0.8 minutes to 6.0 ± 1.8 minutes. None of the cats had vomiting, salivation, or any other adverse effects immediately following administration of these combinations of anesthetics. By 20 minutes after drug administration, surgery was completed in all treatment groups. There were no significant differences among groups in time from injection of the anesthetic combinations to onset of sedation, assumption of lateral recumbency, or start of surgery. The duration of endotracheal intubation was from 5.6 ± 3.4 minutes to 6.4 ± 4.2 minutes for the atipamezole-treated cats and was from 10.0 ± 6.2 minutes to 15.2 ± 8.5 minutes for the saline solution–treated cats. There were also no significant differences among groups in duration of endotracheal intubation or surgery. All cats completed the study and recovered uneventfully from anesthesia and surgery.

Endotracheal intubation could only be achieved in 43% (13/30) of the cats at 10 minutes after the drug administration (Table 1). A significantly (P < 0.01) higher number (n = 7) of cats that received DKBup had signs of an insufficient plane of anesthesia during surgical stimulation and required isoflurane supple-
mentation to attain and maintain a surgical plane of anesthesia, compared with cats in the DKBut (1) and DKH (2) treatment groups. Mean duration of isoflurane supplementation was short (between 2 and 4.3 minutes), and the isoflurane percentage used was 1.5% for maintenance of anesthesia in all cases. Overall, there were no significant differences in intubation, anesthesia, recovery, and postoperative pain scores (Table 2) among treatment groups.

Anesthesia induction to conclusion of surgery—

In the first 19 minutes after drug administration, heart rate decreased significantly to 26% to 33%, 16% to 25%, and 28% to 33% of the baseline values beginning at 6 minutes after DKBut, DKH, and DKBup injection, respectively (Figure 1). There was no significant difference in the decrease in heart rate among treatment groups. Thereafter, heart rates were well maintained (range, 98 to 158 beats/min) in all treatment groups. The lowest heart rates were in saline solution–treated cats, compared with atipamezole–treated cats, with 111.6 ± 14.6 beats/min at 40 minutes in the DKBup–saline solution group, 98.7 ± 3.7 beats/min at 60 minutes in the DKBut–saline solution group, and 105.7 ± 8.5 beats/min at 65 minutes in the DKH–saline solution group. Bradycardia was defined as a heart rate < 80 beats/min and was not observed during the study. No cardiac arrhythmias were noted at any time.

Arterial blood pressures had a biphasic pattern (Figures 2–4). There was a significant increase in mean arterial blood pressure to 20% to 28%, 14% to 30%, and 24% to 25% from the baseline values during the first 20 minutes for DKBut, DKH, and DKBup groups, respectively. Mean arterial blood pressures were significantly higher in the DKBut–atipamezole–treated cats at 10 and 15 minutes after drug administration than for cats in other treatment groups. Thereafter, the mean arterial blood pressure decreased but remained > 75 mm Hg, except in 1 cat in the DKBup–atipamezole group for which mean arterial blood pressure was 67 mm Hg at 20 minutes.

The baseline respiratory rates were significantly higher in the DKBup–saline solution (72.0 ± 13.7 breaths/min) and DKBup–saline solution (77.6 ± 17.3 breaths/min) groups than all the other treatment groups. The respiratory rates decreased from the baseline recorded rate (animal awake) and subsequently remained within the reference range for anesthetized cats (25 to 41 breaths/min; Figure 5). The DKBup–saline solution group had significantly higher respiratory rates (49.8 ± 12.4 breaths/min) at 6 minutes after drug administration than all the other treatment groups. Thereafter, there were no significant differences in respiratory rates among treatment groups. End-tidal partial pressure of CO₂ (recorded only in cats that were intubated) were mildly increased (range, 38 to 57 mm Hg; data not shown) indicating some mild respiratory depression in all the treatment groups. Hypoxemia with SpO₂ < 90% (range, 85% and 89%) was detected in 2 cats in the DKBut group, 1 cat in the DKH group, and 1 cat in the DKBup group. The hypoxemia occurred within the first 5 minutes after drug administration, and oxygen was supplemented until these cats maintained their SpO₂ > 95%. The duration of 100% oxygen sup-
plementation, either via face mask or via endotracheal tube, was between 5 and 10 minutes. All cats responded to 100% oxygen supplementation with an increase and maintenance of SpO₂ > 95%.

Recovery period with and without atipamezole treatment—Overall, heart rates did not change significantly among treatment groups and were maintained between 99 and 126 beats/min during the recovery period. Although atipamezole-treated cats had higher heart rates than the saline solution–treated cats during the first 3 to 5 minutes after atipamezole administration (Table 3), the only significantly higher heart rates among groups were recorded at 20 minutes in the DKBut-atipamezole–treated cats (Figure 1). Mean arterial blood pressure did not change significantly over time during recovery and was maintained between 80 and 122 mm Hg (Figure 3) in all groups, except in the DKBut-atipamezole–treated cats. This group of cats had significantly higher systolic, diastolic, and mean arterial blood pressures than all other treatment groups (Figures 2–4). Body temperatures were maintained between 37.67°C and 38.61°C (99.8° and 101.5°F) for all cats throughout the study. There was no significant difference among groups with regard to body temperature.

Speed of recovery and recovery quality—Atipamezole administration significantly shortened the duration of recovery time in all the treated cats (Table 4), compared with that of saline solution–treated cats. All the atipamezole-treated cats were able to recover to sternal recumbency between 5.6 ± 1.1 minutes and 12.0 ± 1.0 minutes and maintained a standing position between 6.0 ± 1.3 minutes and 13.4 ± 0.9 minutes after IM injection of atipamezole. In contrast, saline solution–treated cats did not recover to standing until between 70.0 ± 5.8 minutes and 101.0 ± 32.1 minutes after saline solution administration. There was no significant difference in recovery duration (time from reversal

| Table 3—Mean ± SEM values for cardiovascular variables obtained 5 minutes after atipamezole or saline solution was administered IM at the conclusion of surgery in the same cats as in Table 1. |
|-----------------|--------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Treatment group | HR (beats/min)     | SAP (mm Hg)     | MAP (mm Hg)     | DAP (mm Hg)     | RR (breaths/min) |
| DKBut-A         | 169.0 ± 26.8³      | 176.3 ± 22.5³   | 138.7 ± 16.2³   | 119.7 ± 15.9³   | 38.0 ± 3.5³      |
| DKBut-S         | 114.6 ± 18.9³      | 141.8 ± 7.1³    | 122.8 ± 15.5³   | 113.2 ± 14.8³   | 30.6 ± 1.9³      |
| DKH-A           | 146.8 ± 14.0³      | 119.2 ± 14.9³   | 92.2 ± 13.6³    | 78.6 ± 13.6³    | 35.2 ± 1.6³      |
| DKH-S           | 118.8 ± 1.38²      | 140.0 ± 2.4³    | 117.0 ± 12.0³   | 105.4 ± 12.0³   | 26.8 ± 3.6³      |
| DKBut-A         | 178.0 ± 32.1³      | 102.7 ± 12.0³   | 76.0 ± 11.0³    | 62.7 ± 10.5³    | 31.7 ± 8.3³      |
| DKBut-S         | 118.8 ± 11.0³      | 138.2 ± 8.2³    | 106.4 ± 9.5³    | 94.6 ± 10.6³    | 38.4 ± 6.5³      |

³Within a column, values with different superscript letters differ significantly (P < 0.05).
DAP = Diastolic arterial blood pressure. HR = Heart rate. MAP = Mean arterial blood pressure. RR = Respiratory rate. SAP = Systolic arterial blood pressure.
See Table 1 for remainder of key.

| Table 4—Mean ± SEM intervals for various anesthetic end points in the same cats as in Table 1. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Treatment group | Postoperative injection to sternal recumbency (min) | Sternal recumbency to standing (min) | Postoperative injection to postoperative injection (min) | Initial anesthetic injection to postoperative injection (min) |
| DKBut-A         | 8.6 ± 1.1³      | 2.8 ± 1.5³      | 11.36 ± 0.7³   | 16.6 ± 1.2      | 28.0 ± 1.5³     |
| DKBut-S         | 59.0 ± 24.0³    | 23.2 ± 8.4³     | 82.2 ± 20.5³   | 17.4 ± 2.3      | 122.8 ± 21.5³   |
| DKH-A           | 12.0 ± 1.0³     | 1.4 ± 0.5³      | 13.4 ± 0.9³    | 19.8 ± 2.6      | 29.2 ± 1.0³     |
| DKH-S           | 53.0 ± 32.2³    | 8.0 ± 5.1³      | 101.0 ± 32.1³  | 23.4 ± 5.5      | 124.4 ± 31.7³   |
| DKBut-A         | 5.6 ± 1.1³      | 1.0 ± 0.5³      | 6.0 ± 1.3³     | 19.6 ± 1.4      | 28.6 ± 4.2³     |
| DKBut-S         | 67.0 ± 5.4³     | 3.0 ± 1.5³      | 70.0 ± 5.8³    | 18.0 ± 1.3      | 85.8 ± 6.5³     |

³Postoperative injection refers to IM administration of atipamezole or saline solution at the conclusion of surgery.
See Tables 1 and 2 for remainder of key.
injection to standing) in saline solution–treated cats among treatment groups. Recovery was uneventful for all animals. Despite the reversal of dexmedetomidine with atipamezole, no dissociative adverse effects such as muscle trembling, salivation, head shaking, vocalization, or defecation were observed after atipamezole administration. None of the cats had signs of pain or required rescue analgesia during the 3 hours of postoperative monitoring.

**Discussion**

The results of this study showed that the 3 dexmedetomidine-ketamine–opioid anesthetic combinations rapidly induced lateral recumbency within 5 minutes following a single IM injection in cats. This result is similar to the report by Selmi et al. in which cats treated with dexmedetomidine (10 µg/kg) alone or in combination with either ketamine (5 mg/kg) or butorphanol (0.2 mg/kg) assumed lateral recumbency within 5 minutes following drug administration. Based on the results of these studies, the duration from injection to onset of lateral recumbency is likely to be dependent on the dexmedetomidine dose and is not altered with the addition of butorphanol or ketamine. In addition, the lack of a significant time difference among treatment groups in inducing lateral recumbency suggests that the receptor class (µ-κ-receptor agonist [hydromorphone], µ-opioid receptor antagonist and κ-receptor agonist [butorphanol], or partial µ-receptor agonist [buprenorphine]) of the opioids did not matter.

The dexmedetomidine dose used in this study (25 µg/kg, IM) was lower than the manufacturer-labeled dose (40 µg/kg) for dexmedetomidine used alone in cats. Slingsby and Taylor reported that to induce analgesia in cats with dexmedetomidine alone, a dose of 40 µg/kg is necessary. These authors also suggested that if a lower dose of dexmedetomidine is used, an additional analgesic is required. In the present study, we combined dexmedetomidine (25 µg/kg) with ketamine and an opioid for castration in cats.

Although these combinations were able to rapidly induce lateral recumbency uniformly in the cats, only 13 of 30 (43%) could be orotracheally intubated. This indicated that the depth of anesthesia was not profound enough to permit acceptance of the endotracheal tube with these anesthetic combinations within 10 minutes after IM administration. Because the number of cats that could not be intubated was nearly identical among treatment groups, it was concluded that there was no difference in terms of opioid receptor class in enhancing endotracheal intubation. A previous study in cats demonstrated that dexmedetomidine (10 µg/kg) induced sedation and that muscle relaxation was enhanced when combined with either ketamine or butorphanol. However, no endotracheal intubation was attempted in that study.

During the surgery, there was a significantly higher number of cats (7/10) in the DKBup group that required isoflurane supplementation, compared with the DKBut and DKH groups. This fact indicates that dexmedetomidine-ketamine together with buprenorphine induces a less reliable depth of anesthesia than when dexmedetomidine-ketamine was combined with butorphanol or hydromorphone. There are several possible explanations for the insufficient surgical plane of anesthesia in the DKBup group. The most probable reason is the delayed onset of action of the buprenorphine following administration. Buprenorphine is known to have a slow onset of action. In a skin thermal antinociception test in cats, buprenorphine (20 µg/kg, IM) was found to have an onset of analgesia at 35 minutes that lasted for 7 to 8 hours. In the present study, it is likely that the onset of buprenorphine-induced analgesia was yet to be reached when the surgical incision started between 10 and 14 minutes after injection, resulting in inadequate analgesic contribution to the anesthetic combination. In contrast, the time to onset of analgesia of butorphanol and hydromorphone were shorter, and only 1 and 2 cats, respectively, required isoflurane supplementation for castration surgery with the same doses of dexmedetomidine and ketamine. Furthermore, buprenorphine has a less sedative and anesthetic-sparing effect in cats. In a study evaluating buprenorphine administration with or without dexmedetomidine in cats, it was found that buprenorphine (10 and 20 µg/kg, IM) did not produce sedation in cats, whereas dexmedetomidine (20 and 40 µg/kg, IM) induced profound sedation. In a study on dogs comparing dexmedetomidine-buprenorphine and dexmedetomidine-butorphanol for hip joint radiography, it was found that dexmedetomidine-buprenorphine induced poor sedation and was not recommended for such a procedure. The lack of contribution of sedation from buprenorphine in these cats likely weakened the total anesthetic effect of the DKBup combination, compared with the other 2 combinations. The analgesic effects of dexmedetomidine-ketamine and the less-than-peak analgesic effects of buprenorphine were not able to produce a surgical plane of anesthesia at 10 minutes.

Along the same line of reasoning, the more rapid onsets of butorphanol and hydromorphone contributed analgesic properties to the drug combination. Consequently, the combination provided sufficient anesthesia for surgical stimulation in the treated cats. It is possible that if surgery had been delayed for an additional 10 minutes in the DKBup group to allow buprenorphine to reach its peak effect, the depth of anesthesia could have been improved for the castration procedure. This result was observed in our previous study in dogs where surgery started 20 minutes after the administration of a dexmedetomidine-ketamine and buprenorphine combination and consistently allowed castration. Alternatively, had we increased the dose of dexmedetomidine from 25 to 40 µg/kg, IM, in combination with ketamine and an opioid, castration of the cats may have been completed without the aid of isoflurane. With the protocol used in the present study, practitioners would either have to allow more time for onset of adequate anesthesia or offer additional anesthesia by providing inhalant supplementation or injectable anesthetics to cats before completing the surgery. Further studies are needed to determine whether DKBup-treated cats require more time or additional analgesia to achieve a surgical plane of anesthesia.

In a previous study, the vomiting response was frequently observed in most cats when dexmedetomidine...
(2 to 40 \(\mu\)g/kg, IM) was administered. In the present study, none of the cats vomited when dexmedetomidine was combined with ketamine and an opioid. We hypothesize that these drug combinations induced anesthesia rapidly and suppressed the vomiting center of these cats. Although there were significant decreases in heart rates at 5 minutes after the dexmedetomidine-ketamine-opioid administration from the awake baseline values, the heart rates were well maintained in all the cats throughout the study. In a previous study\(^7\) in dogs that received similar dexmedetomidine-ketamine-opioid combinations, some of the dogs’ heart rates decreased to approximately 50% to 60% from the baseline to a low range between 45 and 55 beats/min. It is interesting to note that the heart rate of the cats did not become as bradycardic as that of dogs following dexmedetomidine-ketamine-opioid administration. This heart rate difference is likely the result of species differences in the response to dexmedetomidine anesthetic combinations. In another study\(^7\) on sedation in cats, the lowest heart rate observed with dexmedetomidine (10 \(\mu\)g/kg, IM) in combination with butorphanol (0.2 mg/kg) was 64 beats/min and occurred 54 minutes after drug administration, whereas the lowest heart rate observed in the dexmedetomidine and dexmedetomidine-ketamine group comparison was 92 and 88 beats/min, respectively.\(^7\) In the present study, the heart rates were better maintained despite the higher dose of dexmedetomidine. There are several possible reasons for this. Ketamine is known to increase heart rate, so the ketamine component of the combination treatment in this study may have influenced the maintenance of a high heart rate. Another important component of this study is the influence of surgical stimulation on heart rate. Also, it is possible that hydromorphone, as an opioid full \(\mu\)-receptor agonist, may induce a higher vagal tone and therefore may be expected to cause a lower heart rate than either butorphanol or buprenorphine in these cats. However, this was not observed during the study. We concluded that a combination of ketamine and surgical stimulation most probably attenuated the vagal effect of these opioids.

The significantly higher baseline respiratory rates observed in the DKBup–saline solution and DKBut–saline solution groups, compared with the other treatment groups, may have been the result of excitement or stress in these cats. This excitement or stress could have reduced the efficacy of the dexmedetomidine and, combined with a slower onset of the analgesic effect of buprenorphine, resulted in more DKBup-treated cats needing isoflurane supplementation. The findings that the cats in the DKBup–saline solution group had significantly higher respiratory rates even at 6 minutes after drug administration support the conclusion that this group was not well anesthetized at this time.

Hypoxemia was observed in a small percentage of the cats in each of the treatment groups during the first 5 minutes after drug administration. The hypoxic cats responded well to 100% oxygen supplementation. The hypoxic response was likely due to anesthetia-induced respiratory depression. Supplemental oxygen is strongly recommended for cats anesthetized with these injectable anesthetic protocols.

Most of the cats receiving buprenorphine required isoflurane (7/10) administration to attain adequate anesthesia and therefore also received oxygen supplementation. This makes the comparisons in hypoxemia between the groups less useful during the surgery. However, isoflurane supplementation was only necessary during surgery and further need of oxygen supplementation was not required > 20 minutes after administration of these drugs.

The blood pressure of the cats in this study increased initially following the administration of the dexmedetomidine-ketamine-opioid combinations. This increase was likely due to vasoconstriction induced by dexmedetomidine.

In private practice, it is common that the cat be sent home the same day of the castration. We chose to administer atipamezole to evaluate the speed and quality of recovery. The mean time from injection of atipamezole to standing position was between 6 and 14 minutes. It was a mean of 1 hour longer if the cat did not receive atipamezole as a reversal agent. This indicated that IM administration of atipamezole promptly and effectively reversed the effects of dexmedetomidine and significantly shortened the recovery time in atipamezole-treated cats, compared with saline solution–treated cats. Furthermore, in this study, we used only 3 mg of ketamine/kg as part of the combination. This low dose of ketamine allowed cats to receive atipamezole to antagonize the effects of dexmedetomidine without signs of a rough recovery (i.e., ketamine hangover).

In the saline solution control cats, it is interesting to note that the duration of time from initial anesthetic injection to recovery to standing was shortest with the DKBup group (85.8 ± 6.5 minutes), compared with the DKBut (122.6 ± 21.5 minutes) and DKH (124.4 ± 31.7 minutes) groups. The lack of sedative effects of buprenorphine in cats has been previously demonstrated\(^4\) and could have accounted for the shorter recovery time in the DKBup-treated cats. Atipamezole reversed the effects of dexmedetomidine in the dexmedetomidine-ketamine-opioid combinations, which allowed the cats’ heart rates to return to baseline values. Compared with those of the saline solution–treated cats, these heart rates were significantly higher. The blood pressures were significantly higher following atipamezole administration in the DKBup-atipamezole–treated cats than in cats that received atipamezole in the other main treatment groups. The reason for the higher blood pressure is unknown. There was no significant difference in heart rate, respiratory rate, and blood pressures among treatment groups for cats that received saline solution. This suggests that there was no significant difference between opioid types with regard to cardiorespiratory variables during the recovery period in these cats.

Regarding the buprenorphine-treated cats that received atipamezole immediately after surgery, some may argue that these cats did not have analgesia because the buprenorphine had not reached its full effect. Although buprenorphine did not reach its peak effect by 20 minutes, some analgesic property of buprenorphine would have been active as well as meloxicam and ketamine at the time of atipamezole administration.
In summary, all 3 opioids were suitable for combination use with dexmedetomidine-ketamine for anesthesia induction and immobilization of cats. However, the dexmedetomidine-ketamine in combination with butorphanol or hydromorphone tended to have immediate synergistic effects, compared with buprenorphine for castration. If the timing of surgery is to occur quickly (ie, within 10 to 14 minutes after drug administration) with DKBup, a backup plan of inhalant supplementation or injectable anesthesia is required to complete the surgery. Atipamezole administration for anesthetic reversal shortened the recovery time without inducing adverse effects. We recommend dexmedetomidine-ketamine combined with either butorphanol or hydromorphone as an injectable anesthetic combination for castration in cats commencing at 10 minutes after drug administration. Oxygen supplementation is strongly recommended when these injectable anesthetic protocols are used.

  d. Hydromorphone, Baxter Health Care Corp, Deerfield, Ill.
  e. Buprenorphine, Hospira Inc, Lake Forest, Ill.
  g. Metacam, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
  h. Pulse oximeter, PC-VetGuard Plus, Mill Creek, Wash.
  i. ECG, PC-VetGuard Plus, Mill Creek, Wash.
  j. IRMA, PhaseIV, Danderyd, Sweden.
  k. PC-VetGuard Plus, Mill Creek, Wash.
  m. PROC MIXED, SAS, version 9.1, SAS Institute Inc, Cary, NC.

### Appendix 1
Criteria used for intubation scoring.

<table>
<thead>
<tr>
<th>Intubation score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Difficult intubation, and tube cannot be retained; tight jaw tone accompanied by chewing motion; strong tongue withdrawal</td>
</tr>
<tr>
<td>2</td>
<td>Easy intubation with slight coughing or swallowing reflex following intubation but no gagging reflex; relaxed jaw tone; no chewing motions; slight tongue withdrawal</td>
</tr>
<tr>
<td>3</td>
<td>Rapidly becomes anesthetized; good muscle relaxation; intubation easily achieved without coughing, gagging, or tongue withdrawal</td>
</tr>
</tbody>
</table>

### Appendix 2
Criteria used for sedation-anesthesia quality.

<table>
<thead>
<tr>
<th>Sedation-anesthesia score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Active; aware of the surrounding environment; minimal sedation</td>
</tr>
<tr>
<td>1</td>
<td>Mild to moderate sedation with reduced activity only; does not assume sternal or lateral recumbency</td>
</tr>
<tr>
<td>2</td>
<td>Moderate sedation; mildly aware of the surrounding environment; sternal recumbency only</td>
</tr>
<tr>
<td>3</td>
<td>Profound sedation; eyes drooping; head down; inactive; sternal or lateral recumbency; tight jaw tone and unable to be intubated</td>
</tr>
<tr>
<td>4</td>
<td>Rapid smooth induction of anesthesia; no movement; rapidly assumes lateral recumbency with profound muscle relaxation; loose jaw tone and easy intubation</td>
</tr>
</tbody>
</table>

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**References**


Continued on next page.
Appendix 3
Criteria used for anesthetic recovery quality.

<table>
<thead>
<tr>
<th>Recovery score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prolonged struggling; unable to stand without assistance; hyperkinesis in response to manual assistance; increased rectal temperature associated with increased struggling resulting in increased metabolism</td>
</tr>
<tr>
<td>2</td>
<td>Some struggling; repeated attempts to stand and requires assistance to stand; very unstable when walking and unable to maintain balance; some signs of rough recovery (ie, residual effects of anesthetic)</td>
</tr>
<tr>
<td>3</td>
<td>Some struggling; requires some assistance to stand; able to maintain balance once standing; minimal signs of residual effects of anesthetic</td>
</tr>
<tr>
<td>4</td>
<td>Assumes sternal recumbency with little or minimal struggling; stands and walks with minimal effort; no signs of residual effects of anesthetic</td>
</tr>
</tbody>
</table>

Appendix 4
Criteria used for behavioral pain scoring following castration.

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (minimal pain)</td>
<td>Relaxed; resting comfortably; no vocalizing; purring; freely moving and calm; sleeping comfortably; responsive to calm voice and stroking</td>
</tr>
<tr>
<td>2 (faint pain)</td>
<td>Minimally agitated; resting quietly; some body position changes; responsive to calm voice and stroking; minimal signs of pain when handled</td>
</tr>
<tr>
<td>3 (mild pain)</td>
<td>Mildly agitated; some body position shifting; responsive to calm voice and stroking; some salivation; may avoid gentle touching or stroking</td>
</tr>
<tr>
<td>4 (moderate pain)</td>
<td>Moderately agitated; vocalizing; excessive salivation; depressed; some vomiting; muscle trembling; frequent body position changes; some thrashing; may be aggressive; guarding surgical wound upon palpation; not responsive to calm voice or stroking</td>
</tr>
<tr>
<td>5 (severe pain)</td>
<td>Severely agitated; aggressive; vomiting or defecation; vocalizing; excessive salivation; head tossing; violent thrashing; not responsive to calm voice or stroking; may require manual restraint to prevent self-injury</td>
</tr>
</tbody>
</table>

From this month’s AJVR

Plasma disposition, concentration in the hair, and anthelmintic efficacy of eprinomectin after topical administration in donkeys
Cengiz Gokbulut et al

Objective—To investigate plasma disposition, concentration in the hair, and anthelmintic efficacy of eprinomectin after topical administration in donkeys.

Animals—12 donkeys naturally infected with strongyle nematodes.

Procedures—The pour-on formulation of eprinomectin approved for use in cattle was administered topically to donkeys at a dose of 0.5 mg/kg. Heparinized blood samples and hair samples were collected at various times between 1 hour and 40 days after administration. Samples were analyzed via high-performance liquid chromatography with fluorescence detection. Fecal strongyle egg counts were performed by use of a modified McMaster technique before and at weekly intervals for 8 weeks after treatment.

Results—Plasma concentration and systemic availability of eprinomectin were relatively higher in donkeys, compared with values reported for other animal species. Concerning the anthelmintic efficacy against strongyle nematodes, eprinomectin was completely effective (100%) on days 7 and 14 and highly effective (> 99%) until the end of the study at 56 days after treatment. No abnormal clinical signs or adverse reactions were observed for any donkeys after treatment.

Conclusions and Clinical Relevance—Eprinomectin had excellent safety. The relatively high plasma concentration after topical administration could result in use of eprinomectin for the control and treatment of parasitic diseases in donkeys. (Am J Vet Res 2011;72:1639–1645)