Asian small-clawed otters (Aonyx cinereus) are one of the most commonly exhibited otter species in North American zoos and aquaria. These animals require regular veterinary care for evaluation of renal function, dental disease, and contraception. These examinations are generally performed on anesthetized otters to decrease stress on the animal and to ensure staff safety. Historically, a combination of ketamine and midazolam has been recommended for anesthesia in this species, but the use of ketamine has been associated with hyperthermia in otters, which in rare cases has been fatal. One report associated ketamine with profound bradycardia and apnea in a giant otter (Pteronura brasiliensis), making a ketamine-free protocol attractive for animals in this taxon. In addition, ketamine’s anesthetic effects are not reversible, requiring redistribution, metabolism, and excretion for cessation of effect. The development of a fully reversible anesthetic cocktail is advantageous for use in otters for 2 major reasons. First, there are inherent risks to releasing recently anesthetized otters back into an aquatic environ-

**Comparison of anesthesia with fully reversible dexmedetomidine-butorphanol-midazolam versus ketamine-midazolam in captive Asian small-clawed otters (Aonyx cinereus)**

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**Objective**—To evaluate the efficacy and safety of a combination of dexmedetomidine, butorphanol, and midazolam administered IM for anesthesia in captive Asian small-clawed otters (Aonyx cinereus) and to compare this combination with a combination of ketamine and midazolam.

**Design**—Prospective crossover study.

**Animals**—10 captive Asian small-clawed otters.

**Procedures**—A combination of either dexmedetomidine (0.03 mg/kg [0.014 mg/lb]), butorphanol (0.2 mg/kg [0.091 mg/lb]), and midazolam (0.15 mg/kg [0.068 mg/lb]) or ketamine (10.1 mg/kg [4.59 mg/lb]) and midazolam (0.3 mg/kg [0.14 mg/lb]) was administered IM to otters for immobilization to allow scheduled wellness examinations. Otters were intubated and administered 100% oxygen during the examination. Anesthesia was supplemented with isoflurane in oxygen if necessary. Routine medical procedures, including blood collection, radiography, echocardiography, dental scaling, vaccinations, and contraception administration, were performed as indicated during the immobilization. Physiologic, clinicopathologic, and anesthetic variables were recorded and compared. Otters given dexmedetomidine-butorphanol-midazolam were administered atipamezole (0.2 mg/kg [0.091 mg/lb]), naltrexone (0.6 mg/kg [0.27 mg/lb]), and flumazenil (0.05 mg/kg [0.023 mg/lb]) IM at the completion of the examination.

**Results**—The need for and duration of isoflurane administration were greater for ketamine-midazolam anesthesia, compared with dexmedetomidine-butorphanol-midazolam anesthesia. Recoveries were shorter and subjectively smoother with dexmedetomidine-butorphanol-midazolam. Heart rates were significantly higher during ketamine-midazolam anesthesia. Regardless of protocol, all otters developed hypothermia and hypercapnia during anesthesia.

**Conclusions and Clinical Relevance**—Both protocols were safe and effective for this species, but the reversible nature of dexmedetomidine-butorphanol-midazolam resulted in more rapid recoveries than did ketamine-midazolam. Otters anesthetized with ketamine-midazolam may require additional anesthetic medications for routine examinations, and assisted ventilation and thermal support may be of benefit with either protocol. (J Am Vet Med Assoc 2014;244:107–114)
ment. The ability to completely reverse the effects of anesthetic drugs lessens this concern. Second, it is desirable to return otters to their social group as soon as possible after anesthesia to reduce the potential for aggression during reintroduction. A completely reversible anesthetic protocol can provide a rapid recovery without the ataxia and lethargy often seen for a few hours after ketamine-based anesthetic protocols\(^8\) and would allow animals to be reunited with their social group almost immediately after anesthetic events.

Medetomidine, a selective \(\alpha_2\)-adrenoreceptor agonist, is a tranquilizer commonly used in anesthetic protocols for nondomestic carnivores.\(^8,9\) It is often used with a cyclohexane such as ketamine or a cyclohexane-benzodiazepine combination such as tiletamine-zolazepam.\(^3,10\) It is suitable for IM injection and has the advantage of being rapidly reversible with atipamezole. However, the use of medetomidine in dogs and other carnivores is associated with initial hypertension and decreased cardiac output and bradycardia caused by vasoconstriction.\(^11,12\)

Butorphanol, a mixed agonist-antagonist opioid, is often used in combination with medetomidine or ketamine for its sedative and analgesic properties.\(^13,14\) Its effects can be reversed with naloxone or naltrexone. Midazolam, a water-soluble benzodiazepine tranquilizer, is also commonly used in anesthetic combinations for its muscle relaxant and anticonvulsant properties.\(^2,14\) Flumazenil is used to reverse the effects of benzodiazepines, including midazolam.\(^15\) Both butorphanol and midazolam may cause respiratory depression in some species.\(^15\)–\(^17\)

A combination of medetomidine-butorphanol-midazolam produces an anesthetic state in dogs that resembles that produced by inhalation anesthesia.\(^18\) The 3 drugs have synergistic effects and therefore can induce a more profound depth of anesthesia than could be produced by any of the drugs used alone. Both medetomidine and butorphanol have analgesic effects. Furthermore, the combination can be completely reversed by IM administration of atipamezole, naltrexone, and flumazenil. Reports\(^10\)–\(^12\) have been published on the use of this combination for patas monkeys (\(Erythrocebus patas\)), ring-tailed lemurs (\(Lemur catta\)), California sea lions (\(Zalophus californianus\)), and African lions (\(Panthera leo\)). A similar protocol that replaced midazolam with diazepam for red wolves (\(Canis lupus rufus\)) has been described.\(^15\)

On the basis of studies where medetomidine-butorphanol-midazolam has been compared with other protocols containing ketamine, the medetomidine-butorphanol-midazolam combination produces a superior recovery and does not have appreciable anesthetic disadvantages.

Dexmedetomidine, the S-enantiomer of medetomidine, is responsible for medetomidine’s effects as an \(\alpha_2\)-adrenoreceptor agonist.\(^24\) Based on its chemical structure, the effects of dexmedetomidine should be nearly identical to those of racemic medetomidine when given at half the dose\(^24\); however, very few published reports describe its use in nondomestic species. The purpose of the study reported here was to evaluate the anesthetic and cardiopulmonary effects of 2 anesthetic combinations used for annual examinations of captive Asian small-clawed otters. Specifically, we wanted to compare a dexmedetomidine-butorphanol-midazolam combination followed by anesthetic reversal with atipamezole, naltrexone, and flumazenil with ketamine-midazolam, a protocol previously used for Asian small-clawed otters at Zoo Atlanta and the Georgia Aquarium.

### Materials and Methods

**Animals and study protocol**—The project was approved by the Zoo Atlanta Scientific Review Committee and the Georgia Aquarium Research Committee. All animals were anesthetized as part of their regularly scheduled wellness examinations. Otters were anesthetized with one protocol the first year and the other protocol the second year. Because of differences in husbandry practices between the 2 institutions, assignment of anesthetic protocol was not randomized by individual; instead, each day was designated a ketamine-midazolam day or a dexmedetomidine-butorphanol-midazolam day, and all otters anesthetized on that day were administered the same protocol. The following year, otters were administered the other protocol regardless of which day they were handled. One collection consisted of 5 full female siblings, and the other collection consisted of a pair and 2 litters of their offspring. In all, 4 male and 10 female otters were available for inclusion, with ages ranging from 3.9 to 17.8 years.

Food was withheld from otters for approximately 12 hours prior to the administration of anesthesia. Otters underwent anesthesia by IM administration of dexmedetomidine\(^e\) (0.03 mg/kg [0.014 mg/lb]), butorphanol\(^b\) (0.2 mg/kg [0.091 mg/lb]), and midazolam\(^c\) (0.15 mg/kg [0.068 mg/lb]) or by IM administration of ketamine\(^d\) (0.1 mg/kg [4.59 mg/lb]) and midazolam (0.3 mg/kg [0.14 mg/lb]). If necessary, isoflurane in 100% oxygen was administered by facemask and subsequently by endotracheal tube to deepen anesthesia or prolong immobilization. Those otters that did not require isoflurane were nonetheless endotracheally intubated and placed on 100% oxygen. At the end of all procedures, the otters anesthetized with dexmedetomidine-butorphanol-midazolam received IM administration (each in a separate syringe) of atipamezole\(^f\) (0.2 mg/kg), flumazenil\(^g\) (0.05 mg/kg [0.023 mg/lb]), and either naltrexone\(^h\) (0.6 mg/kg [0.27 mg/lb]; \(n = 16\)) or naloxone\(^i\) (0.1 mg/kg [0.05 mg/lb]; 4).\(^14\)

Otters were restrained in either a net or a squeeze cage for manual injection of anesthetic drugs. Anesthetic agents were mixed in a single syringe and administered IM in a caudal limb or epaxial muscle mass with a 20-gauge needle attached to a 3-mL syringe. After initial injection, the animals were placed in a dark, quiet crate for anesthetic induction. Time of initial anesthetic effect (defined as decreased reactivity to stimuli), time to sternal recumbency, and total time to induction of anesthesia (defined as a lack of righting response and a lack of response to manual stimulation) were recorded. Once anesthesia had been induced, otters were endotracheally intubated and instrumented with a rectal temperature probe to measure body temperature, ECG leads, a pulse oximeter probe, and a \(CO_2\) monitor. Blood pressure was measured indirectly with an oscillometric blood pressure monitor\(^1\) and a size \(\frac{7}{4}\) or \(\frac{5}{4}\) cuff placed on the tail. A forced air warmer blanket\(^2\) was placed on any animal for which body temperature decreased to \(< 37.8^\circ\text{C} (100^\circ\text{F})\). Mechanical ventilation was not performed during the examination, although occasional
breaths were administered by hand approximately once per minute. Clinical variables (body temperature, heart rate, respiratory rate, \(\text{SpO}_2\), blood pressure, and \(\text{PETCO}_2\)) were recorded at 5-minute intervals throughout anesthesia. If isoflurane was required for completion of the examination, the delivered percentage of isoflurane was recorded, in addition to the duration of administration.

Procedures performed on all otters included endotracheal intubation, complete physical examination, venous blood collection for CBC and serum biochemical analysis, arterial blood collection from the coccygeal artery for arterial blood gas analysis,1 echocardiography, and abdominal and thoracic radiography. Procedures performed for some but not all otters included subcutaneous contraceptive implantation, abdominal ultrasonography, vaccination against canine distemper virus and rabies virus, direct ophthalmoscopy, dental radiography, and dental cleaning.

When all procedures were completed, animals were placed in a carrier and provided with supplemental heat via a forced air warmer. Otters anesthetized with dexmedetomidine-butorphanol-midazolam were given reversal agents as noted. All otters were then closely monitored, and relevant time points were recorded, including extubation, first head lift (stage 2 [heavy sedation]), when the otter became sternal and was able to ambulate in the carrier (stage 1 [light sedation]), and full recovery (no ataxia and able to follow moving objects with eyes).

**Statistical analysis**—Analyses were performed with the aid of software. Normality was tested with the Kolmogorov-Smirnov test. To facilitate comparisons, each animal’s mean body temperature, heart rate, respiratory rate, and MAP were calculated for each 15-minute period throughout anesthesia. In addition, each animal’s mean heart rate, respiratory rate, and MAP for the entire procedure were calculated. Also, the mean \(\text{SpO}_2\) for each animal was calculated as well as the duration that each animal’s \(\text{SpO}_2\) was < 95%. Comparisons of mean anesthetic variables, physiologic values, CBC, and chemistry values were performed by means of paired \(t\) tests or repeated-measures ANOVA as appropriate, and a Bonferroni correction was applied when indicated. Relationships between variables were evaluated on the basis of linear regression and Pearson correlations. Values of \(P < 0.05\) were considered significant.

**Results**

Twenty-four anesthetic events were recorded; 20 of these were paired events and included in the study. One otter that received dexmedetomidine-butorphanol-midazolam and another that received ketamine-midazolam died prior to the subsequent scheduled wellness examinations when each would have received the opposite protocol; one died as a result of a viral infection and the other as a result of a bacterial infection. Two otters received dexmedetomidine-butorphanol-midazolam but were not in the collection or not available for sampling during the previous set of wellness examinations.

Both dexmedetomidine-butorphanol-midazolam and ketamine-midazolam resulted in rapid anesthetic induction (Table 1). With the exception of 1 otter during an unpaired event, all ketamine-midazolam–anesthetized otters required isoflurane for intubation, so duration of immobilization provided solely by the injectable drugs was impossible to compare. Only 3 dexmedetomidine-butorphanol-midazolam events required isoflurane to prolong anesthesia, so only those corresponding ketamine-midazolam events were included in relevant statistical analyses. Both the duration of isoflurane administration required and the mean delivered isoflurane percentage were significantly greater for ketamine-midazolam procedures, despite the smaller number of comparisons available. Total anesthesia time (defined as initial injection to recovery to stage 1), time from the end of the procedure (defined either as the time reversal agents were given [dexmedetomidine-butorphanol-midazolam] or the time the otter was placed in a recovery carrier [ketamine-midazolam] or the time the otter was placed in a carrier and provided with supplemental heat via a forced air warmer), and other variables were significantly different between anesthesia protocols.

**Table 1**—Paired comparisons for anesthetic variables of 10 captive Asian small-clawed otters (Aonyx cinereus) anesthetized with either dexmedetomidine-butorphanol-midazolam or ketamine-midazolam in a crossover study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine-butorphanol-midazolam</th>
<th>Ketamine-midazolam</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of first injection of anesthetic drugs to initial effects (min)</td>
<td>1.9 ± 0.9 (1–4)</td>
<td>2.2 ± 2.8 (1–10)</td>
<td>0.774</td>
</tr>
<tr>
<td>Time of first injection of anesthetic drugs to recurrency (min)</td>
<td>2.7 ± 1.5 (1–6)</td>
<td>5.6 ± 6.7 (1–24)</td>
<td>0.243</td>
</tr>
<tr>
<td>Total anesthetic time (min)</td>
<td>86.0 ± 23.8* (57–118)</td>
<td>110.9 ± 26.5* (63–148)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time from end of procedure to stage 2 sedation (min)</td>
<td>1.5 ± 0.5* (1–2)</td>
<td>7.10 ± 6.8* (1–22)</td>
<td>0.032</td>
</tr>
<tr>
<td>Time from end of procedure to stage 1 sedation (min)</td>
<td>2.6 ± 2.2* (1–7)</td>
<td>35.7 ± 19.0* (14–67)</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of isoflurane administration† (min)</td>
<td>37.7 ± 28.9* (0–71)</td>
<td>91.0 ± 17.3* (76–110)</td>
<td>0.022</td>
</tr>
<tr>
<td>Isoflurane delivered‡ (%)</td>
<td>0.75 ± 0.25* (0.5–1.0)</td>
<td>1.4 ± 0.17* (0.75–1.5)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Data are mean ± SD (range).

*Within rows, values are significantly \((P < 0.05)\) different from one another. †Only 3 dexmedetomidine-butorphanol-midazolam events required isoflurane, so comparisons were made with only those pairs. ‡The end of the procedure was defined as the time reversal agents were given (for dexmedetomidine-butorphanol-midazolam anesthesia) or the time the otter was placed in a recovery carrier (for ketamine-midazolam anesthesia). Stage 2 sedation was defined as heavy sedation and was recorded as beginning with the first head lift; stage 1 was defined as light sedation and was recorded when the otter positioned itself in sternal recurrency.
in the recovery carrier (ketamine-midazolam) to stage 2 sedation, and time from the end of the procedure to stage 1 sedation were significantly shorter for dexmedetomidine-butorphanol-midazolam anesthesia, compared with ketamine-midazolam anesthesia.

One otter that appeared to be fully anesthetized was handled at 9 minutes after the injection of dexmedetomidine-butorphanol-midazolam. However, at 13 minutes after initial injection, the otter aroused during instrumentation attempts, jumped off the table and ran across the room before coming to rest. After 6 additional minutes with no stimulation, the otter appeared completely anesthetized and was retrieved, intubated, and instrumented without administration of supplemental anesthetic agents. Two otters anesthetized with dexmedetomidine-butorphanol-midazolam and 1 otter anesthetized with ketamine-midazolam were suspected to have received only partial initial injections and required supplementation. One of the otters anesthetized with dexmedetomidine-butorphanol-midazolam was supplemented with dexmedetomidine (0.006 mg/kg [0.0027 mg/lb], IM), and the other was supplemented with dexmedetomidine (0.007 mg/kg [0.0032 mg/lb]), butorphanol (0.12 mg/kg [0.054 mg/lb]), and midazolam (0.07 mg/kg [0.032 mg/lb]) IM; neither required additional injectable agents nor isoflurane. The otter anesthetized with ketamine-midazolam received a supplemental IM injection of ketamine (4.45 mg/kg [2.023 mg/lb]) and midazolam (0.15 mg/kg [0.0682 mg/lb]) and required isoflurane for intubation and the remainder of the immobilization.

Body temperature decreased at least 0.5°C (1.4°F) during all anesthetic events, and the final body temperature at the end of anesthesia was < 38°C (100.4°F) in all but 1 anesthetic event (Figure 1). Mean ± SD body temperatures were significantly (P < 0.001) different for the dexmedetomidine-butorphanol-midazolam protocol between the first (38.3 ± 1.2°C [100.9 ± 2.2°F]) and fourth (36.0 ± 1.1°C [96.7 ± 2.1°F]) 15-minute period, and mean body temperatures were also significantly (P < 0.001) different for the ketamine-midazolam protocol between the first (38.3 ± 0.6°C [101.0 ± 1.1°F]) and fourth (36.3 ± 1.0°C [97.4 ± 1.7°F]) 15-minute period. The mean body temperatures for each 15-minute period were not significantly different between the 2 protocols. Subjectively, body temperatures decreased more quickly with dexmedetomidine-butorphanol-midazolam anesthesia, but although total body temperature decrease was greater for dexmedetomidine-butorphanol-midazolam events (2.4 ± 0.83°C [4.3 ± 1.5°F]) than for ketamine-midazolam events (2.0 ± 0.94°C [3.6 ± 1.7°F]), this difference was not significant (P = 0.483). The decrease in body temperature was not related to the duration of anesthesia (r² = –0.044; P = 0.881), the duration of isoflurane anesthesia (r² = –0.037; P = 0.674), or the mean body temperature during the first 15 minutes of anesthesia (r² = 0.067; P = 0.118).

Mean SpO₂ did not differ significantly (P = 0.218) between dexmedetomidine-butorphanol-midazolam (97.4 ± 1.7%) and ketamine-midazolam (96.0 ± 2.0%) protocols, and the duration that SpO₂ was < 95% was small and similar (P = 0.322) for both dexmedetomidine-butorphanol-midazolam (4.1 ± 6.6 minutes) and ketamine-midazolam (7.6 ± 5.4 minutes) protocols. On the other hand, heart rates differed significantly between protocols, overall, and at every period measured (Figure 1). Within protocols, heart rates did not differ between the first and fourth 15-minute anesthetic periods.
Respiratory rates also decreased during anesthesia (Figure 1), but neither the mean respiratory rate for each 15-minute anesthetic period nor the overall mean respiratory rate for the entire procedure differed between protocols. Despite the overall decrease, there were no significant differences between periods within either protocol. Although both MAP (Figure 2) and PETCO$_2$ tended to be higher during dexmedetomidine-butorphanol-midazolam anesthesia, no significant differences between protocols were detected. Blood pressure and PETCO$_2$ were not measured before the second 15-minute period, so results are available for only 3 periods. Blood pressure tended to increase during ketamine-midazolam anesthesia and decrease during dexmedetomidine-butorphanol-midazolam anesthesia; these changes were not significant for ketamine-midazolam anesthesia; however, for dexmedetomidine-butorphanol-midazolam anesthesia, MAP was significantly ($P < 0.001$) higher in the second 15-minute period (90.3 ± 18.2 mm Hg) versus the third (75.3 ± 11.4 mm Hg) and fourth (72.9 ± 12.3 mm Hg) 15-minute periods. During ketamine-midazolam anesthesia, the oscillometric blood pressure monitor was frequently unable to obtain a reading; only 4 otters had blood pressure readings during all of the 15-minute periods, whereas for dexmedetomidine-butorphanol-midazolam anesthesia, readings were obtained during all periods for all 10 otters.

Arterial blood samples were collected for blood gas analysis at a mean of 41 ± 18 minutes after the start of anesthesia with the dexmedetomidine-butorphanol-midazolam protocol and 46 ± 13 minutes after the start of anesthesia with the ketamine-midazolam protocol ($P = 0.40$). Marked respiratory acidosis was present during all anesthetic events, regardless of protocol. No significant differences were found in pH, PaCO$_2$, base excess, HCO$_3^-$ concentration, total CO$_2$ concentration, or lactate concentration between the 2 treatments (Table 2). Despite all otters receiving 100% oxygen via endotracheal tube, PaCO$_2$ was significantly different between protocols. The PaCO$_2$ was always higher than the PETCO$_2$ at the time of arterial blood collection.

Results of CBC and serum biochemical analyses were all within expected ranges for the species. No significant differences were seen in otters between the 2 protocols. Although α$_2$-adrenoreceptor agonists are known to cause hyperglycemia, the mean glucose concentration was not significantly ($P = 0.288$) different between the ketamine-midazolam (86.4 ± 14.1 mg/dL [4.80 ± 0.783 mmol/L]) and dexmedetomidine-butorphanol-midazolam (106.2 ± 12.5 mg/dL [5.89 ± 0.694 mmol/L]) protocols.

**Discussion**

Both dexmedetomidine-butorphanol-midazolam and ketamine-midazolam resulted in safe, effective immobilization for the Asian small-clawed otters in this study. Dexmedetomidine-butorphanol-midazolam anesthesia was remarkable for rapid and smooth recoveries; this was similar to findings in ring-tailed lemurs and lions anesthetized with medetomidine-butorphanol-midazolam. Although most procedures could likely have been performed with either protocol, when ketamine-midazolam was used, the anesthetic plane was not deep enough to allow endotracheal intubation without supplemental isoflurane anesthesia. Subjectively, it was also noted that otters produced copious oral secretions with ketamine-midazolam, further complicating intubation. Anesthetic inductions were rapid and smooth with both protocols. As noted by others, it is important to wait a full 10 minutes after anesthetic induction with medetomidine-butorphanol-midazolam before handling animals to avoid spontaneous arousal. One otter had a prolonged recovery with evidence of dysphoria after its ketamine-midazolam anesthesia.

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**Figure 2**—Mean ± SD arterial blood pressure (MAP) of captive Asian small-clawed otters anesthetized with either dexmedetomidine-butorphanol-midazolam (triangles) or ketamine-midazolam (circles) in a crossover study. Within protocols, significantly different means are marked with different letters. There were no significant differences between protocols.

**Table 2**—Mean ± SD values for arterial blood gas variables in captive Asian small-clawed otters (n = 7) anesthetized with either dexmedetomidine-butorphanol-midazolam or ketamine-midazolam in a crossover study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine-butorphanol-midazolam</th>
<th>Ketamine-midazolam</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of anesthesia when the</td>
<td>41.4 ± 18.2</td>
<td>46.1 ± 12.6</td>
<td>0.404</td>
</tr>
<tr>
<td>blood sample was taken (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.188 ± 0.04</td>
<td>7.187 ± 0.042</td>
<td>0.926</td>
</tr>
<tr>
<td>PaCO$_2$ (mm Hg)</td>
<td>70.5 ± 7.7</td>
<td>70.6 ± 7.2</td>
<td>0.985</td>
</tr>
<tr>
<td>Paco$_2$ (mm Hg)</td>
<td>453 ± 152*</td>
<td>556 ± 58*</td>
<td>0.029</td>
</tr>
<tr>
<td>Base excess (mmol/L)</td>
<td>–1.43 ± 0.98</td>
<td>–1.57 ± 0.98</td>
<td>0.689</td>
</tr>
<tr>
<td>HCO$_3^-$ (mmol/L)</td>
<td>26.7 ± 1.2</td>
<td>26.6 ± 0.6</td>
<td>0.944</td>
</tr>
<tr>
<td>Total CO$_2$ (mmol/L)</td>
<td>28.6 ± 1.3</td>
<td>28.7 ± 0.8</td>
<td>0.786</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.54 ± 0.6</td>
<td>0.31 ± 0.23</td>
<td>0.305</td>
</tr>
</tbody>
</table>

*Within rows, values are significantly ($P < 0.05$) different from one another.
event, characterized by swaying movements from side to side, occasional vocalizations, and an exaggerated startle reflex. The same otter had a normal recovery from anesthesia with dexmedetomidine-butorphanol-midazolam.

Early in the study, naloxone was used to reverse butorphanol in the dexmedetomidine-butorphanol-midazolam protocol (n = 4), but after concerns that 1 otter appeared ataxic and lethargic 2 hours after apparent full recovery, the longer-acting opioid antagonist naltrexone was used for subsequent dexmedetomidine-butorphanol-midazolam events. Lethargy or sleepiness after apparent full recovery was not noted for any other anesthetic event, so it is unknown whether this incident was a result of an insufficient duration of action of naloxone or just an idiosyncratic reaction. Given the known duration of action of butorphanol in other carnivores, naloxone should have been appropriate for reversal.15,20 However, pharmacokinetics have not been determined for butorphanol in Asian small-clawed otters, so it is unknown whether this drug has a duration of activity > 2 to 4 hours, as is typical in other species.

The small size of Asian small-clawed otters may make them more susceptible to hypothermia rather than hyperthermia, which has been reported in other otter species anesthetized with ketamine.2,3 Although dexmedetomidine is known to cause body temperature to decrease,27 in the present study, anesthesia with both dexmedetomidine-butorphanol-midazolam and ketamine-midazolam resulted in hypothermia, despite the use of a circulating warm water blanket and a forced air warmer blanket. The results of this study as well as the reports in the literature illustrate the importance of closely monitoring body temperature in anesthetized otters and being prepared to intervene with mechanisms to either cool or warm the otters.

Overall, mean respiratory rates decreased during anesthesia, but trends were different for all otters, and the practice of periodically providing manual breaths to the otters confounded the analysis of respiratory rates. The hypventilation was reflected in the respiratory acidosis documented on arterial blood gas analysis. The degree of hypventilation seen in this study is concerning for long-term anesthetic maintenance with either protocol without the ability to administer intermittent positive pressure breaths or, at the very least, the ability to provide supplemental oxygen to offset hypoxemia that can result from high alveolar concentrations of CO₂ in patients breathing room air.

The PetCO₂ also reflected hypventilation and was higher than optimal for anesthetized mammals.28 Such pronounced hypventilation was not reported in red wolves anesthetized with medetomidine-butorphanol-diazepam.21 Patas monkeys anesthetized with medetomidine-butorphanol-midazolam had normal mean PetCO₂ early in the anesthetic period, but PetCO₂ gradually increased and reached 50 to 60 mm Hg by 20 minutes after induction of anesthesia.39 The PetCO₂ was not measured in the present study until approximately 30 minutes following anesthetic induction, and given the progressive decrease in respiratory rate, may reflect a similar scenario of hypventilation increasing over time. The use of supplemental isoflurane in the otters anesthetized with ketamine-midazolam may have contributed to the hypventilation in these animals.

In the present study, manual positive pressure ventilation was initiated for otters with PetCO₂ > 65 mm Hg at PetCO₂ below this pressure, positive pressure ventilation appeared to result in breath-holding behavior. In addition, although Asian small-clawed otters are not deep divers, as aquatic mammals they may tolerate higher CO₂ concentrations than terrestrial mammals.29 This reduced sensitivity to CO₂ allows diving animals to remain submerged for prolonged periods but also results in a decreased respiratory drive during anesthesia-related hypercapnia.29 A recent study on hippopotami (Hippopotamus amphibious) anesthetized with medetomidine-ketamine found PetCO₂ as high as 80 mm Hg in some animals; those authors associated this with the dive response.

All otters in the present study had respiratory acidosis at the time of the blood gas sampling; hypventilation as a result of anesthesia-related respiratory depression was considered the most likely cause. The PaCO₂ was high, compared with that of terrestrial species anesthetized with similar drug protocols.20,22 Giant otters anesthetized with medetomidine-ketamine had a PaCO₂ ranging from 48 to 61 mm Hg, which is intermediate between that reported in the literature for other species4 and that in the Asian small-clawed otters of this report. However, the time of arterial blood collection was not reported in that study,4 and the total anesthesia time for the giant otters was less than that for the Asian small-clawed otters of the present study. If, as expected, hypventilation and acidosis progressed with time, PaCO₂ for the giant otters may have been higher later in anesthesia. The PaCO₂ did not indicate major problems with oxygenation in the Asian small-clawed otters of the present study, but this is likely a result of the use of 100% oxygen for maintenance, and predictions cannot be made regarding the use of these anesthetic protocols in otters breathing only room air.

Although the MAP was higher during dexmedetomidine-butorphanol-midazolam anesthesia, there was not a significant difference between treatments, and otters were not hypertensive as might be expected with α₂-adrenoreceptor agonists.14,15,31 However, this result should be interpreted with caution, considering that we did not measure MAP before the second 15-minute period of anesthesia, and during dexmedetomidine-butorphanol-midazolam anesthesia, the earliest measured MAPs were significantly higher than when measured subsequently. If hypertension occurred early in anesthesia, as might be expected with dexmedetomidine, it could have been missed in this study.

Heart rates were greater during ketamine-midazolam anesthesia, compared with dexmedetomidine-butorphanol-midazolam anesthesia, which is not surprising given the expected hemodynamic effects of these drugs.15 During dexmedetomidine-butorphanol-midazolam anesthesia, heart rates were often in the range of 60 to 70 beats/min, whereas for ketamine-midazolam anesthesia, the lowest mean heart rate during a 15-minute period was 146 beats/min. Despite the low heart rates, otters did not appear to be hemodynamically compromised during dexmedetomidine-butorphanol-midazolam anesthesia; other variables remained within reference limits, and there were no indications

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of problems during or after recovery. α2-Adrenoceptor agonists are known to cause bradycardia, which may be an appropriate physiologic response to a transient increase in systemic vascular resistance.13 Heart rates of giant otters anesthetized with ketamine and medetomidine range from 60 to 65 beats/min,7 although giant otters are larger than Asian small-clawed otters and may be expected to have lower resting heart rates. Marine otters (Lontra felina) are approximately the same size as Asian small-clawed otters and, when anesthetized with ketamine and medetomidine, had heart rates of 119 to 146 beats/min,10 which are higher than the heart rates of the Asian small-clawed otters of the present study. However, several of the marine otters were undergoing surgery for radiotracker implantation, so manipulation of abdominal contents or pain may have resulted in higher heart rates than would be expected during less invasive procedures. The low heart rates in Asian small-clawed otters during dexmedetomidine-butorphanol-midazolam anesthesia were likely a result of a cardiovascular response to increased systemic vascular resistance and less sympathetic stimulation than in the otters that received ketamine-midazolam. A field study comparing the administration of medetomidine-ketamine with that of medetomidine-midazolam in golden jackals (Canis aureus) found that those that received medetomidine-ketamine had a significantly higher heart rate. In addition, in the Asian small-clawed otters of the present study, the absence of painful stimuli and heart rate. In addition, in the Asian small-clawed otters during dexmedetomidine-butorphanol-midazolam anesthesia were likely a result of a cardiovascular response to increased systemic vascular resistance and less sympathetic stimulation than in the otters that received ketamine-midazolam. A field study comparing the administration of medetomidine-ketamine with that of medetomidine-midazolam in golden jackals (Canis aureus) found that those that received medetomidine-ketamine had a significantly higher heart rate. In addition, in the Asian small-clawed otters of the present study, the absence of painful stimuli and the synergy of butorphanol and dexmedetomidine may have contributed to lower heart rates.18

This study had several limitations. The use of animals that were part of active collections meant that the schedule and timing of immobilizations were dictated by the preventive health needs of the otters, not the precepts of study design. It would have been ideal to continue to use naltrexone for all immobilizations to document whether additional otters had a period of reedation, but the switch to naltrexone, a longer-acting drug, was made to avoid exposing otters to undue risk following reintroduction to their social group and to an aquatic exhibit. Similarly, these facilities continually strive to improve their husbandry practices, but improvements could introduce bias in the study. For example, 1 institution built a squeeze cage for Asian small-clawed otters between the first and second set of anesthetic events. In the first set of immobilizations, otters were transferred from a carrier to a net for their initial injection. Because the animal care staff felt that the squeeze cage was a considerable improvement over the net, they felt that it was inappropriate to go back to use of a net for the second set of immobilizations. Also, because otters were from 2 institutions, there were differences in standard operating procedures, husbandry practices, and equipment that could have introduced bias. Although the use of a crossover design should have eliminated the effects of most of these differences, the lack of standardization was not ideal. Another limitation is genetic. All of the otters within each collection were closely related (all littermates from one institution, and a parent and offspring—all full siblings—at the other). Finally, the investigators in the present study were not blinded to the anesthetic protocol for each otter.

Dexmedetomidine-butorphanol-midazolam anesthesia in captive Asian small-clawed otters offered 2 main advantages over ketamine-midazolam anesthesia: excellent muscle relaxation sufficient for endotracheal intubation and a rapid, smooth recovery permitting nearly immediate return to the aquatic environment and the social group. Further investigation of the dexmedetomidine-butorphanol-midazolam protocol for other otter species, particularly North American river otters (Lontra canadensis), is warranted, given the known disadvantages of ketamine-based protocols for those species. The hypercapnia in the study otters was concerning, especially because it was not easily remedied with increased ventilation. Although these otters did not develop any apparent ill effects from the hypercapnia, more studies are needed to better elucidate the relationship between respiratory drive and CO2 concentration in anesthetized diving mammals.

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