Use of a medetomidine-ketamine combination for anesthesia in captive common hippopotami (Hippopotamus amphibius)

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Objective—To establish an anesthetic protocol suitable for surgical interventions in hippopotami (Hippopotamus amphibius).

Design—Prospective case series.

Animals—10 adult male hippopotami undergoing castration.

Procedures—A combination of medetomidine (60 to 80 μg/kg [273 to 36.4 μg/lb]) and ketamine (1 mg/kg [0.45 mg/lb]) was administered IM on the basis of mean estimated weights of 1,330 ± 333 kg (2,926 ± 733 lb; median, 1,350 kg [2,790 lb]; range, 900 to 2,000 kg [1,990 to 4,400 lb]). Monitoring included sequential blood gas analyses, pulse oximetry, and capnography. Reversal of anesthesia with atipamezole (0.34 ± 0.06 mg/kg [0.15 ± 0.027 mg/lb]; median, 0.33 mg/kg [0.15 mg/lb]; range, 300 to 500 mg total dose) was uneventful and rapid in all cases.

Results—Complete immobilization and a surgical anesthetic plane were achieved 27 ± 11.8 minutes (median, 24.5 minutes [range, 14 to 44 minutes]) after initial injection. Anesthesia (97.3 ± 35.3 minutes; median, 95 minutes [range, 57 to 188 minutes]) was maintained with 3.4 ± 2.2 (median, 3) additional doses of ketamine (0.1 to 0.4 mg/kg [0.045 to 0.18 mg/lb]). Transitory apnea of 4.71 ± 2.87 minutes (median, 4 minutes [range, 1 to 9 minutes]) was documented in 5 animals. Apnea during anesthesia was viewed as a physiologic condition in this semiaquatic mammal because related vital parameters (heart rate, pH, peripheral hemoglobin oxygen saturation as measured by pulse oximetry, venous partial pressure of CO₂, and lactate and HCO₃ concentrations) remained unchanged and did not differ significantly than those parameters for the 5 animals with continuous respiration.

Conclusions and Clinical Relevance—Both in captivity and in the wild, common hippopotami are difficult to anesthetize. The combination of medetomidine and ketamine provided an excellent surgical plane of anesthesia and a self-limiting dive response. (J Am Vet Med Assoc 2012;241:110–116)

Common hippopotami (Hippopotamus amphibius) are difficult to anesthetize. Both the unique morphology and physiology of the hippopotamus constitute an anesthetic challenge. The thick skin and dense subcutaneous tissue can impede darting and the resorption and distribution of anesthetic agents. Difficulties because of their large size, dive reflex, arousal during anesthesia, and limited vascular access have been previously reported.1–3 Generally, reports on anesthesia of hippopotami are rare. A literature search of PubMed and Scopus with keywords such as “anesthesia (or immobilization) AND hippopotamus amphibious” or “anesthesia (or immobilization) AND common or Nile hippo” resulted in only 1 publication.2 Several case reports1–5 have been published in conference proceedings or summarized in books. Most reports2–8 on chemical restraint provide descriptions of immobilizations during field capture or case reports with differing protocols. The most commonly used anesthetic is the potent opioid etorphine, sometimes in combination with xylazine or acepromazine.1,2,8,9 Reported complications with these opioid-based anesthetic combinations include apnea, cyanosis, bradycardia, and fatal respiratory arrest.10 In a retrospective study,2 6 of 16 immobilizations resulted in complications from bradypnea and apnea. In 3 of 4 cases, these respiratory complications were successfully resolved by administration of doxapram, a respiratory stimulant. In the same study2 of 16 procedures, only 2 provided an anesthetic depth sufficient for surgical interventions.

The use of detomidine and butorphanol has been reported as a sole anesthetic protocol and for anesthetic

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induction but only for minor nonsurgical procedures.\(^3\)\(^-\)\(^5\) Spontaneous arousal of animals following stimulation makes this protocol suitable for deep sedation but for noninvasive procedures only. The purpose of the study reported here was to establish a reliable and safe anesthetic protocol suitable for longer procedures and surgical interventions in hippopotami, with a combination of medetomidine and ketamine. Additionally, we sought to determine species-specific effects of anesthesia in common hippopotami.

### Materials and Methods

#### Animals

Ten captive adult male common hippopotami were included in the study. The animals were held at various zoological gardens in Europe and the Middle East (Zoo de La Palmyre, Les Mathes, France \([n = 1]\); Safari Thoiry, Thoiry, France \([n = 1]\); Zoological Center Tel Aviv, Ramat Gan, Israel \([n = 6]\); Vienna Zoo, Vienna, Austria \([n = 1]\); and Pecs Zoo, Pecs, Hungary \([n = 1]\]). All animals were surgically castrated for population or behavioral control reasons. All procedures were conducted according to the guidelines of the ethics committee of the University of Veterinary Medicine, Vienna, and the respective legislation in the countries where the procedures were performed. Following inquiry, no diseases were reported in any of the 10 hippopotami and all appeared healthy at the preoperative clinical evaluation. All animals were isolated in a separate pen for the procedure. Food but not water was withheld on the day of the procedure.

#### Procedures

Anesthesia was induced with a combination of medetomidine\(^6\) (60 to 80 μg/kg [27.3 to 36.4 μg/lb] and ketamine\(^7\) (1 mg/kg [0.45 mg/lb]) administered IM at the base of the ear with a CO\(_2\)-propelled remote dart system\(^2\) and 3- or 5-mL\(^2\) darts with a 2.0 × 100-mm reinforced needle.\(^1\) Animals with sufficient anesthetic depth (ie, no response or movement to acoustic and physical stimulation, assessment of pupil dilation, loss of palpebral reflex and pain, and presence of corneal reflex) after anesthetic induction were safely approached. After wedging the mouth open with a wood block, a peripheral venous catheter\(^8\) was placed in a sublingual vein and a constant flow of saline (0.9% NaCl) solution\(^9\) (1 to 2 mL/kg/h [0.45 to 0.9 mL/lb/h]) was provided. The sublingual paramedian veins were found to be the most reliable for rapid vascular access. In 1 animal, a palmar medial digital vein was used for venous access because no adequate sublingual vein was found. The ventral tail vein and the palmar medial digital vein were used for blood collection in most animals.

The hippopotami were rolled into a right lateral recumbent position to provide access to the inguinal region for castration. With the hippopotamid recumbent, additional oxygen was supplied via nasal insufflation at a rate of 10 to 15 L/min. Anesthesic monitoring included evaluation of RR by observing thoracic excursions. Spontaneous arousal of animals following stimulation makes this protocol suitable for deep sedation but for noninvasive procedures only. The purpose of the study reported here was to establish a reliable and safe anesthetic protocol suitable for longer procedures and surgical interventions in hippopotami, with a combination of medetomidine and ketamine. Additionally, we sought to determine species-specific effects of anesthesia in common hippopotami.

The 10 hippopotami had a mean age of 5.5 ± 5.24 years (median, 5 years; range, 2 to 14 years) and a mean estimated weight of 1,330 ± 333 kg (2,926 ± 732.6 lb; median, 1,350 kg [2,970 lb]; range, 900 to 2,000 kg [1,980 to 4,400 lb]). Because the exact weights of the animals were unknown, drug doses of medetomidine (60 to 80 μg/kg) and ketamine (1 mg/kg) were administered on the basis of the estimated weights.

Drug doses for anesthesia induction were 91.0 ± 17.8 mg (median, 90 mg; range, 60 to 120 mg) of medetomidine and 1,330 ± 333.3 mg (median, 1,350 mg; range, 900 to 1,500 mg) of ketamine, IM.

Twelve minutes after administration of the initial drug combination, the anesthetic effect was assessed.
ZOO ANIMALS (no response or movement to acoustic and physical stimulation before approaching, assessment of pupil dilation, loss of palpebral reflex and pain response, and presence of corneal reflex). Five animals went into sternal recumbency and had sufficient anesthetic depth to be safely approached, thereby allowing establishment of venous access and the start of surgery. In 4 animals, supplemental doses of medetomidine (25 ± 10.8 mg; median, 22.5 mg; range, 15 to 40 mg) and ketamine (406.3 ± 153.3 mg; median, 400 mg; range, 225 to 600 mg) administered IM were necessary to achieve recumbency and a sufficient plane of anesthesia. In 1 animal, medetomidine (245 mg) and ketamine (3,450 mg) had to be given IM before an acceptable anesthetic plane was reached.

The required repeated application of supplemental doses in this specific animal was due to extremely difficult darting conditions. Because of restriction in fire line and extensive movement of the animal in the enclosure, the animal could not be adequately darter at the ear base; therefore, only partial resorption and distribution of anesthetic agents were likely.

The mean induction time from initial dart injection to sternal or lateral recumbency was 27 ± 11.8 minutes (median, 24.5 minutes; range, 14 to 44 minutes). A sufficient plane of anesthesia was easily maintained throughout the surgical castration procedure with small supplemental IV administrations of ketamine (150 to 500 mg/bolus), which equates to a mean ketamine administration of 0.007 ± 0.002 mg/kg/min (0.0032 ± 0.001 mg/lb/min; median, 0.006 mg/kg/min [0.0027 mg/lb/min]; range, 0.002 to 0.010 mg/kg/min [0.001 to 0.0045 mg/lb/min]). Two animals were given an additional dose of 20 mg medetomidine, IV. Anesthesia was reversed at 57 to 188 minutes (mean time of procedure, 97.3 ± 35.3 minutes; median, 95 minutes) after the initial dart, with 300 to 500 mg of atipamezole (mean, 0.34 ± 0.06 mg/kg [0.15 ± 0.027 mg/lb]; median, 0.33 mg/kg [0.15 mg/lb]). Atipamezole was administered IV (n = 2) and, to prevent an extremely rapid arousal, partly IV and partly IM (n = 8). Recovery was uneventful and rapid, with a mean recovery time of 4.8 ± 2.86 minutes (median, 3.5 minutes; range, 2 to 10 minutes).

The venous blood gas data in the 10 hippopotami showed a mean pH of 7.32 ± 0.05 (median, 7.32), mean \( P_{\text{vCO}_2} \) of 67.54 ± 13.94 mm Hg (median, 71.22 mm Hg), mean lactate concentration of 2.81 ± 1.43 mmol/L (median, 2.71 mmol/L), and mean \( HCO_3^- \) concentration of 34.98 ± 6.82 mmol/L (median, 36.59 mmol/L) during the course of anesthesia. With the exception of 2 animals, all blood gas values were derived from venous blood samples. Therefore, \( P_{\text{aO}_2} \) and arterial oxygen saturation were not included. In 1 animal, it was possible to obtain 3 sequential arterial blood samples. These arterial samples had a mean arterial oxygen saturation of 96.67 ± 4.04% (median, 99.0%; range, 92 to 99%) and \( P_{\text{aO}_2} \) of 122.33 ± 44.64 mm Hg.
(median, 131.0 mm Hg, 74 to 162 mm Hg), with an increase of arterial oxygen saturation from 92% to 99% and increase of \( \text{Pao}_2 \) from 74 to 162 mm Hg over a period of 28 minutes. In all animals, additional oxygen was supplied via nasal insufflation at a rate of 10 to 15 L/min.

The hippopotami had a mean RR of 3.3 ± 3.22 breaths/min (median, 1.5 breaths/min; range, 0 to 15 breaths/min), mean HR of 42.97 ± 15.37 beats/min (median, 36.83 beats/min; range, 17 to 100 beats/min), and mean \( \text{Spo}_2 \) of 79.16 ± 12.38% (median, 84.08%; 4% to 99%) during the course of anesthesia.

Temporary apnea (mean duration, 4.71 ± 2.87 minutes; median, 4 minutes; range, 1 to 9 minutes) was documented in 5 of 10 animals. These apneic phases during anesthesia were viewed as physiologic apnea resulting from a diving behavior and not as a drug-induced effect because related vital parameters remained unchanged and the occurrence of the apneic phase appeared to be spontaneous and not temporally linked to external influences such as ketamine administration. Furthermore, onset of respiration after apnea was spontaneous. Respiratory stimulatory drugs were not administered. Individuals with temporary apnea had a rapid progressive decrease in peripheral \( \text{Spo}_2 \) during apneic phases (time from the last recorded respiration to the onset of respiration; Figure 1). This value returned to within reference range immediately after onset of respiration. The mean of the lowest measured
SpO2 values during the apneic phase was significantly (P < 0.001) lower, compared with the mean SpO2 immediately before apnea commencement and after onset of respiration. Anesthesia time (P = 0.76), body weight (P = 0.93), and age (P = 0.55) of the individual animals did not influence the mean RR. The mean HR during anesthesia was not significantly (P = 0.191) influenced by mean RR (Figure 2) and remained unchanged in all animals despite elevated P\textsubscript{CO2} and low SpO2. A reflexive bradycardia during apneic phases was not recorded. Furthermore, in all animals, mean P\textsubscript{CO2} was not significantly (P = 0.427) elevated with decreasing mean RR, and mean SpO2 did not significantly (P = 0.218) differ with decreasing mean RR. In 7 of 10 animals, both with and without temporary apnea, pH was < 7.35, with animals with temporary apnea having a greater tendency for respiratory acidosis, whereas animals with a higher RR tended to develop metabolic (lactic) acidosis. Nevertheless, mean pH was not significantly (P = 0.492) correlated with mean RR. The associations between mean RR and mean HCO\textsubscript{3}, P = 0.086) as well as mean lactate concentration (P = 0.067) were not significant. Rectal temperature was 36.1\textdegreeC ± 1.69\textdegreeC (97.02\textdegreeF ± 33.0°F; range, 39.5\textdegreeC [91.9\textdegreeF] to 103.1\textdegreeF]). Hyperthermia occurred in only 1 animal (39.5\textdegreeC [103.1\textdegreeF]), most likely because of the long duration of the procedure (188 minutes) as well as the high ambient temperature.

Discussion

In the present study, the combination of medetomidine and ketamine provided an excellent surgical plane of anesthesia and a self-limiting dive response in 10 adult male hippopotami undergoing castration. A dive response is a physiologic response of reptiles, birds, and mammals to submergence, usually involving apnea, bradycardia, and peripheral vasoconstriction. In contrast, a dive reflex is related to historical studies in which the study animals were forcibly submerged and a reflex was induced to prevent drowning. Reports of anesthesia in common hippopotami are rare. Therefore, the use of anesthetic drugs and their resulting effects have previously not been investigated in detail. Respiratory depression is the most common complication reported during anesthesia in hippopotami.\textsuperscript{1,2,5,9} The most common previously used anesthetic, the potent opioid etorphine used alone or in combination with xylazine or acepromazine, has often led to complications such as apnea, cyanosis, bradycardia, and fatal respiratory arrest.\textsuperscript{1,2,5,9} Similar to species with a dive response such as elephant seals (Mirounga leonina), hippopotami have a high sensitivity and low therapeutic index to opioids, resulting in anesthesia-related mortality rates as high as 35%.\textsuperscript{11–13}

Although opioids, especially etorphine, have been widely used for chemical restraint and capture in wildlife and zoological medicine, there are few studies\textsuperscript{14–16} examining and reporting their pharmacokinetic or pharmacodynamic effects in individual species. The pharmacokinetic and pharmacodynamic influences of opioids are largely extrapolated from human studies, experimental animal studies, or domestic animals. Inhibitory effects on the RR, ventilation, and CO\textsubscript{2} sensitivity due to opioid stimulation of the \(\mu\) receptors are known and have been observed during anesthesia.\textsuperscript{17,18} However, different animal species have considerable differences in opioid sensitivity and CNS response.\textsuperscript{14–16,18} Reasons for these different responses are not entirely understood but are presumably related to pharmacokinetic variations as well as differing receptor distribution in various regions of the brain.\textsuperscript{11} Furthermore, as previous authors have noted, the interactions between groups of opioid receptors at various locations as well as interactions between different receptor types within a given location are complex and incompletely understood at this time.\textsuperscript{14}

To avoid the previously reported respiratory depressive effects of opioids during anesthesia in hippopotami, a combination of medetomidine and ketamine was evaluated. In the present study, successful surgical anesthesia in 10 adult males was achieved; however, in 5 of 10 animals, temporary apnea was documented. In previously described anesthesic protocols that included etorphine, respiratory depression had to be treated with respiratory stimulants to avoid a fatal outcome.\textsuperscript{2} In contrast, animals in the present study had a self-limiting apnea, indistinguishable from the physiologic diving apnea of several minutes’ duration in submerged hippopotami.\textsuperscript{10} As such, we described this temporary apnea as a self-limiting dive response in these hippopotami. Despite the significant decrease in SpO2 during the apneic phases of 1 to 9 minutes’ duration, vital parameters such as peripherally measured HR, pH, P\textsubscript{CO2}, and lactate and HCO\textsubscript{3} concentrations remained unchanged in these 5 animals. Furthermore, the extremely low SpO2 during apnea immediately increased to preapneic levels when the animal resumed breathing. The animals did not have a P\textsubscript{CO2}-driven increase in HR, as seen in nonaquatic species. More importantly, mean RR did not significantly influence the mean HR, P\textsubscript{CO2}, pH, SpO2, or lactate and HCO\textsubscript{3} concentrations during anesthesia. In our opinion, this indicates a controlled, physiologically adapted apneic phase derived from natural diving behavior. Nevertheless, the pattern of the dive response in the present study is not consistent with previously described dive responses in other species. Although the term dive reflex is still used in the literature, dive response would be the more correct term because it has been shown that diving mammals have some control over the intensity of the response to submergence.\textsuperscript{20} Reflexive bradycardia, as reported for other diving species during apneic phases,\textsuperscript{20,21} was not seen in the hippopotami of the present study. The dive response in hippopotami as well as related physiologic changes have not been previously investigated. Only 1 anecdotal case report\textsuperscript{22} describes dive-related bradycardia in a 6-minute ECG of a juvenile hippopotamus.

Furthermore, other measured parameters in the hippopotami in the present study reveal major differences when compared with those previously reported for other diving mammals. Result of a previous study indicate that lactate concentrations increase in active deep-diving mammals during the dive period. Contrary to our expectations, mean lactate concentrations did not increase with decreasing mean RR and were actu...
ally lower in the animals with a dive response, compared with the continuously breathing individuals. The short apneic phases in combination with reduced or no movement of the hippopotamus may explain the absence of increased blood lactate concentrations. The normal lactate concentrations would seem to indicate that a switch to anaerobic metabolism does not occur in hippopotami during short apnea, possibly indicating an increased \( O_2 \) storage capacity or other compensatory mechanisms such as hypometabolism or reduced peripheral perfusion, as reported in other diving mammals.\(^2\) It is interesting to note that during dive response events in the animals in the present study, peripherally measured \(\text{SpO}_2\) decreased very rapidly to 41.14 ± 22.40\% (median, 45\%; range, 4\% to 69\%; Figure 1) but HR peripherally measured at the same site remained unchanged. This appears to exclude a simple peripheral shunting mechanism and points to a possible preperipheral oxygen scavenging mechanism as seen in other species. Diving mammals have established various mechanisms to cope with hypoxic states, such as increased \( O_2 \) storing capacity in the blood (increased Hct and blood hemoglobin), muscle (high myoglobin concentrations and high affinity of myoglobin for \( O_2 \)), and lungs (high tidal volume) or higher capillary densities in brain tissue.\(^2\) Increased Hct (> 60\%) and blood hemoglobin concentration (25 g/dL) in deep-diving phocid seals have been reported.\(^2\) In the hippopotami in the present study, an Hct of 42% to 54% (mean, 46.5\%) and hemoglobin concentration of 14.3 to 18.4 g/dL (mean, 15.83 g/dL) were measured. These values are similar to previously reported values for this species and are within the range of values reported in large terrestrial mammals.\(^1\) Myoglobin potentially has a high \( O_2 \) affinity and can serve as an oxygen store. Especially in deep-diving mammals such as hooded seals, very high concentrations of myoglobin in the skeletal muscles have been reported.\(^27,28\) The myoglobin concentration in common hippopotami is unknown but warrants further investigation.

Low RR, apnea, hypercapnia, and possible perfusion-ventilation mismatch due to the large body weight of the animals during recumbency have all been described for hippopotami in previous anesthesia reports.\(^1\) In the present study, hypercapnia was seen both in individuals with and without the dive response. This can be explained by bradypnea, shunting, and possible perfusion-ventilation mismatch because of the large body weight of the animals during lateral recumbency as previously described. Another unique feature in the physiology of diving animals is a high respiratory tidal volume, which enables these animals to rapidly eliminate excess \( CO_2 \) and reload \( O_2 \). In continuously breathing common hippopotami, mean end-tidal partial pressure of \( CO_2 \) has been reported to be 41.7 mm Hg.\(^9\) This value correlates with the values measured in the present study of 40 mm Hg during continuous breathing. In animals that had a dive response, the onset of respiration included an end-tidal partial pressure of \( CO_2 \) rapidly increased to approximately 80 mm Hg and \(\text{SpO}_2\) increased within a few seconds to preapneic levels. These results are indicative of a high tidal volume. Subsequent studies should consider the use of a continuous monitoring system for the vital parameters with a resolution of ≤ 10 seconds to document these rapid changes in respiratory parameters.

In zoo and wildlife medicine, veterinarians are confronted with a wide range of animal species with, at times, vastly differing physiologic characteristics. Collection of additional physiologic data in the future may help explain these mechanisms and their relevance during anesthesia. Generally, it seems prudent, if not essential, to consider evolutionary physiologic differences when performing anesthesia in various wildlife species.

References

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