

**COMPARISON OF BUTORPHANOL-DETOMIDINE  
VERSUS BUTORPHANOL-AZAPERONE FOR THE  
STANDING SEDATION OF CAPTIVE GREATER ONE-  
HORNED RHINOCEROSSES (*RHINOCEROS UNICORNIS*)**

Author(s): Priya Bapodra , B.Vet.Med., M.Sc., Jonathan Cracknell , B.V.M.S,  
Cert. V.A., Cert. Zoo. Med., and Barbara A. Wolfe , D.V.M., Ph.D., Dipl.  
A.C.Z.M.

Source: Journal of Zoo and Wildlife Medicine, 45(1):60-68. 2014.

Published By: American Association of Zoo Veterinarians

DOI: <http://dx.doi.org/10.1638/2013-0066R.1>

URL: <http://www.bioone.org/doi/full/10.1638/2013-0066R.1>

---

BioOne ([www.bioone.org](http://www.bioone.org)) is a nonprofit, online aggregation of core research in the biological, ecological, and environmental sciences. BioOne provides a sustainable online platform for over 170 journals and books published by nonprofit societies, associations, museums, institutions, and presses.

Your use of this PDF, the BioOne Web site, and all posted and associated content indicates your acceptance of BioOne's Terms of Use, available at [www.bioone.org/page/terms\\_of\\_use](http://www.bioone.org/page/terms_of_use).

Usage of BioOne content is strictly limited to personal, educational, and non-commercial use. Commercial inquiries or rights and permissions requests should be directed to the individual publisher as copyright holder.

---

# COMPARISON OF BUTORPHANOL-DETOMIDINE VERSUS BUTORPHANOL-AZAPERONE FOR THE STANDING SEDATION OF CAPTIVE GREATER ONE-HORNED RHINOCEROSSES (*RHINOCEROS UNICORNIS*)

Priya Bapodra, B.Vet.Med., M.Sc., Jonathan Cracknell, B.V.M.S., Cert. V.A., Cert. Zoo. Med., and Barbara A. Wolfe, D.V.M., Ph.D., Dipl. A.C.Z.M.

**Abstract:** Three adult and two subadult greater one-horned rhinoceroses (*Rhinoceros unicornis*) were sedated a total of nine times using two different intramuscular sedative combinations in order to compare the effectiveness of these combinations in inducing consistent standing sedation in this species. The sedation protocols compared were butorphanol tartrate (50–60 mg) and detomidine hydrochloride (20–30 mg; BD) versus butorphanol tartrate (80–120 mg) and azaperone (80–120 mg; BA). Specific doses were adjusted according to age and sex class, and based on previous experience. Parameters compared included time to achieve defined levels of sedation, time to recovery following antagonism, physiological parameters including heart rate, respiratory rate, indirect arterial blood pressure, and venous blood gas values. A hydraulic restraint chute was utilized to mechanically restrain animals during the procedures, and blood collection and ophthalmic examinations were conducted on all animals. Both protocols resulted in standing sedation for  $\geq 22.3 \pm 2.9$  min or until antagonists were administered. The BD protocol resulted in deeper and more consistent sedation, compared to the BA protocol. Naltrexone hydrochloride (250–300 mg) and tolazoline hydrochloride (1,500–2,000 mg) were administered intramuscularly to antagonize protocol BD, whereas naltrexone alone (200–500 mg) was used to antagonize BA. Time to full antagonism, defined as normal mentation and ambulation following administration of antagonists, was prolonged in the BD protocol ( $132.3 \pm 17.2$  min) compared with the BA protocol ( $7.5 \pm 2.5$  min). Venous blood gas analysis did not reveal any significant blood gas deviations during sedation when compared with either conscious equine or white rhinoceros (*Ceratotherium simum*) venous reference ranges. In summary, both combinations resulted in adequate standing sedation for minimally invasive procedures, although BD resulted in more profound and consistent sedation.

**Keywords:** Azaperone, butorphanol tartrate, detomidine hydrochloride, greater one-horned rhinoceros, *Rhinoceros unicornis*, sedation.

## INTRODUCTION

Chemical restraint is an important tool in the medical management of rhinoceroses.<sup>35</sup> Despite improvement in the use of mechanical restraint devices with operant conditioning,<sup>18</sup> chemical restraint is often indicated for untrained or unresponsive individuals, institutions that lack restraint devices, for painful or invasive procedures, or reproductive management.<sup>2,12,42,47</sup> If appropriate, standing sedation is preferable to general anesthesia in rhinoceroses, due to recumbency-associated complications such as progressive atelectasis, pulmonary shunting, weight-related hypoventilation, and resultant ventila-

tion-perfusion mismatching.<sup>17</sup> Additional complications include compression of dependent muscles and nerves or poor positioning resulting in myopathies or neuropathies.<sup>10,40</sup> Despite the common occurrence of greater one-horned rhinoceros (*Rhinoceros unicornis*) in captivity, the high prevalence of foot lesions requiring chronic care,<sup>47</sup> and the numerous reports of general anesthesia in this species,<sup>1,3,5,9,11</sup> there are few reports specifically documenting standing sedation protocols in greater one-horned rhinoceros, many based on assumptions from other rhinoceros species.<sup>5,40,46</sup> However, reports indicate that greater one-horned rhinoceros demonstrate a similar response to anesthetic agents as white rhinoceroses (*Ceratotherium simum*).<sup>35</sup>

Etorphine, an ultrapotent opioid, has been used in Rhinocerotidae to induce a wide range of effects from standing sedation to surgical anesthesia.<sup>5,40</sup> Standing sedation doses of etorphine published for captive greater one-horned rhinoceroses range from 0.5–1.0 mg given intramuscularly (i.m.), with exact doses being determined

From *the Wilds*, 14000 International Road, Cumberland, Ohio 43732, USA (Bapodra, Wolfe); Longleat Safari and Adventure Park, Longleat, Warminster, Wiltshire, BA12 7NJ, United Kingdom (Cracknell). Present address (Bapodra): Columbus Zoo and Aquarium, 9990 Riverside Drive, Powell, Ohio 43065, USA. Correspondence should be directed to Dr. Bapodra (priya.bapodra@columbuszoo.org).

based on the size of the animal and the depth of sedation desired.<sup>5,14</sup> At anesthetic doses, physiological side effects of etorphine include respiratory depression, inhibition of gastrointestinal motility, decreased body temperature, central nervous system excitement, pruritus, tachycardia, and increased blood pressure.<sup>2,13</sup> Similar to other species, opioids use in Rhinocerotidae commonly causes dose-dependent respiratory depression and hypoxia, which is exacerbated by recumbency.<sup>4,17,23,24,30,48</sup> Peripheral vasoconstriction, tachycardia, and resultant severe hypertension have been reported in the white rhinoceroses.<sup>15,24,28,35,37</sup> This clinical response has also been reported following administration of high opioid doses in domestic and exotic equids.<sup>20,24</sup>

The addition of  $\alpha$ -2 agonists to an etorphine protocol may reduce the risk of hypertension through modulation of sympathetic tone, as well as reduce the etorphine dose required for sedation.<sup>28,30</sup>  $\alpha$ -2 agonists provide reliable muscle relaxation and controlled anesthesia when used in combination with opioids in rhinoceroses.<sup>2</sup> The use of etorphine presents a risk to humans, as inadvertent exposure to even small volumes can cause profound and rapid respiratory suppression, and precautions must be taken to avoid accidental opioid exposure.<sup>16,35</sup> To reduce the risk to operators and to reduce the side effects at induction, alternative opioids in combination with other agents have been utilized for rhinoceros sedation. In domestic animals, butorphanol has agonist properties at the  $\kappa$  receptor effecting sedation and analgesia, and weak antagonism at the  $\mu$  receptor, resulting in mild respiratory suppression.<sup>27</sup> This synthetic compound has minimal effects on cardiopulmonary function compared with etorphine.<sup>27</sup> Antagonism of butorphanol is advised following its use in equine patients due to suppression of gastrointestinal motility, although this effect is minor compared to that of other opioids.<sup>20,25,26</sup>

The  $\alpha$ -2 adrenoreceptor agonists are commonly used to induce reliable dose-dependent sedation, analgesia and muscle relaxation, and can be readily antagonized using selective antagonists. Detomidine hydrochloride is primarily used for sedation and analgesia in horses. When combined with an opioid in horses, detomidine produces more reliable sedation.<sup>7</sup> Dose-dependent cardiorespiratory side effects include an immediate increase in arterial pressure due to vasoconstriction, followed by bradycardia and subsequent hypotension, reduced cardiac output and decreased respiratory rate.<sup>30</sup> Highly excited or

fractious animals may require higher doses of detomidine to produce sedation, which increases the severity of the side effects.<sup>30</sup> Finally, detomidine is associated with decreased gastrointestinal motility due to parasympatholytic effects, although the ability to antagonize  $\alpha$ -2 agonists reduces this concern.<sup>26,30,45</sup> The  $\alpha$ -2 agonists have been shown to be particularly useful in rhinoceros anesthesia and sedation.<sup>2,35</sup>

Azaperone, a butyrophenone tranquilizer, has been used as an adjunct to opioid-induced chemical restraint of rhinoceroses, and has been found to reduce the level of mortality and morbidity associated with animal translocations.<sup>5,21,31,35,39-41</sup> Azaperone is approved in the United States for use in swine for sedation and to reduce aggression. Its use results in mild muscle relaxation without analgesia.<sup>30,36</sup> At high doses, extrapyramidal side effects such as tremors, rigidity and catalepsy can occur.<sup>30</sup> Even at low doses, unexpected effects such as excitement have been noted following intravenous use in the horse, and hallucinatory behavior following intramuscular use in the Asian elephant (*Elephas maximus*).<sup>8,43</sup> In a variety of species, azaperone is noted to have depressant effects on the cardiovascular system, resulting in decreased heart rate, cardiac output and arterial blood pressure,<sup>15,36</sup> and impaired thermoregulation.<sup>30,36</sup> In equids and suids, respiratory stimulation has been noted, although pulmonary function is only mildly affected.<sup>30,36</sup> Unfortunately, unlike opioids and  $\alpha$ -2 adrenoreceptor agonists, no specific antagonists exist for azaperone.

Intramuscular butorphanol (0.15 mg/kg) and detomidine (0.03 mg/kg) have been reported to produce standing sedation in a small number of rhinoceroses of unspecified species.<sup>5</sup> This combination has been used i.m. in adult greater one-horned rhinoceroses to facilitate surgical repair of rectal prolapse, and was found to provide excellent sedation, good muscle relaxation, and some analgesia.<sup>3</sup> Butorphanol-detomidine (BD) has also been used in white rhinoceros neonates (0.03 mg/kg and 0.07 mg/kg i.m. respectively) to reliably induce recumbency.<sup>12</sup> Radcliffe and Morke describe the use of i.m. butorphanol (100 mg) and azaperone (100 mg) to induce standing sedation in greater one-horned rhinoceroses, although details of the depth, duration and limitations of this combination were not reported.<sup>40</sup> Butorphanol and azaperone have been used successfully in white rhinoceroses to induce deep sedation and recumbency.<sup>38,39</sup> Although butorphanol-azaperone (BA) combinations are used in

**Table 1.** Summary of animal signalment, sedation and reversal agent doses administered intramuscularly.

Rhino ID	Sex	Age class	Sedatives			Reversal agents	
			Detomidine (mg)	Butorphanol (mg)	Azaperone (mg)	Tolazoline (mg)	Naltrexone (mg)
1	Male	Adult	30	60	—	2,000	300
2	Female	Adult	30	50	—	2,000	250
3	Female	Adult	30	50	—	2,000	250
4	Female	Sub-adult	20	50	—	1,500	250
5	Female	Sub-adult	20	50	—	1,500	250
1	Male	Adult	—	120	120	—	240
2	Female	Adult	—	100	100	—	500
3	Female	Adult	—	100	100	—	200
4	Female	Sub-adult	—	80	80	—	400

rhinoceroses, the potency of this combination is highly variable, producing a range of effects from mild sedation to recumbency. The goal of this study was to compare physiological effects and depth of sedation produced by BD and BA in greater one-horned rhinoceroses.

### MATERIALS AND METHODS

Five captive greater one-horned rhinoceroses underwent a total of nine procedures under standing sedation during a seven-month period. Animals were managed in a 400-acre pasture during the spring and summer, and were housed in barns during the fall and winter months. Diet consisted of a commercial pelleted ration and *ad libitum* mixed grass hay, plus *ad libitum* fresh grass and browse while managed in pasture. Sedation was necessary in these individuals for venipuncture, ophthalmic examination (transpalpebral ultrasonography, tonometry, and conjunctival microbiology), reproductive evaluation and artificial insemination. The group consisted of two subadult females (both 4 yr old, weight estimate 1,500 kg), two adult females (12 and 15 yr old, weight estimate 2,000 kg) and one adult male (8 yr old, weight estimate 2,000 kg). The adult females in the group had received intermittent operant conditioning to enter the restraint chute and tolerate rectal palpation. Access to hay and concentrates were restricted on the morning of procedure days; access to water was not limited.

For induction of sedation, each individual was walked into the hydraulic restraint chute with the front restraint gate closed. Once within the chute, the back restraint gate was closed, and induction drugs were administered by pole syringe ('Cats' Jabstick, Dan-Inject, Austin, Texas 78754, USA) into the neck musculature using a 16-ga, 40-mm hypodermic needle. Five procedures utilized a

combination of butorphanol tartrate (50–60 mg per animal; ZooPharm, 50 mg/ml, Fort Collins, Colorado 80522, USA) and detomidine hydrochloride (20–30 mg per animal; Dormosedan™, 10 mg/ml, Pfizer Animal Health, Exton, Pennsylvania 19341, USA) during the spring (protocol BD) (Table 1). Four subsequent procedures carried out during the fall utilized a combination of butorphanol (80–120 mg per animal) and azaperone (80–120 mg per animal; ZooPharm, 50 mg/ml) (protocol BA).

Following drug administration, each animal was monitored for evidence of defined levels of sedation and anxious individuals were offered small amounts of produce. The first effect of sedation was noted when the animal became less active and alert within the chute (Table 2). Once mild sedation was achieved (defined as altered, stationary stance and mildly altered mentation with spontaneous movement of ears and elevated head), the hydraulic chute was narrowed to restrain the animal without affecting thoracic excursions. At this time, an eye cover was placed over the animal's eyes and novel personnel and equipment were brought into the vicinity of the animal. Moderate sedation was described as a stationary, unbalanced or leaning stance with a lowered head and minimal movement of ears despite tactile stimulation. Deep sedation in this study was defined as recumbency. The level of sedation was evaluated throughout the procedure by monitoring the movement of ears, the animals' head position, and response to tactile stimulation.

Physiological monitoring consisted of rectal body temperature, auricular artery pulse rate or thoracic auscultation of heart rate, respiratory rate, arterial hemoglobin oxygen saturation (SpO<sub>2</sub> Cardell® 9402 Diagnostic Monitor, Midmark Corporation, Versailles, Ohio 45380, USA) and indirect blood pressure monitoring (Cardell®

**Table 2.** Summary of response times (minutes) during standing sedation.<sup>a</sup>

	Butorphanol/detomidine	Butorphanol/azaperone	<i>P</i> value from paired <i>t</i> -test
Mean time to first effect	2.8 ± 0.4 (5)	2.5 ± 1.1 (4)	0.686
Mean time to mild sedation	4.2 ± 0.4 (5)	4.3 ± 1.5 (4)	0.686
Mean time to moderate sedation	7.8 ± 1.2 (5)	5.0 ± 1.0 (2)	0.076
Time between induction and antagonist administration	26.6 ± 4.5 (5)	22.3 ± 2.9 (4)	0.116
Time to show mild sedation after antagonism	5.0 ± 1.4 (5)	3.5 ± 0.5 (2)	0.047
Time to full antagonism	132.3 ± 17.2 (3)	7.5 ± 2.5 (2)	0.034

<sup>a</sup> Mean ± standard deviation. (*n*) = number of animals.

9402 Diagnostic Monitor, Tuff Cuff CR5212 12 cm bladder size, CAS Medical Systems, Inc., Branford, Connecticut 06405, USA). Monitoring which required touching the animal was started as soon the animal reached mild sedation and would tolerate the presence of equipment. SpO<sub>2</sub> was measured on the pinna, lip or anus, vestibular or prepuccial fold, and indirect blood pressure was monitored with the cuff placed around the pinna using recommended methods.<sup>35</sup> Skin over the medial radial vein was scrubbed with an iodophor and alcohol prior to venipuncture. As soon as handling was possible, venous blood was drawn from the medial radial vein into heparinized syringes for immediate blood gas analysis (I-Stat Portable Clinical Analyzer, Heska® Corporation, Loveland, Colorado 80538, USA; VetScan I-Stat CG8+ Cartridges, Abaxis Inc., Union City, California 94587, USA).

Antagonists were administered once veterinary procedures were concluded. Butorphanol was antagonized with intramuscular naltrexone hydrochloride (two to five times the dose of butorphanol, ZooPharm, 50 mg/ml) (Table 1). Detomidine was antagonized using intramuscular tolazoline hydrochloride (1mg/kg estimated, Tolazine®, 100mg/ml, Lloyd Laboratories, Shenandoah, Iowa 51601, USA). The time from antagonist administration to various stages of recovery was noted (Table 2). Animals were released from mechanical restraint when no or mild sedation (alert, minimal ataxia) was demonstrated, and walked back to their stall. Time to full antagonism was noted when the animals showed normal mentation and ambulation, and no discernable clinical signs of sedation were present. Animals were given immediate access to hay, water and conspecifics (if housed with another animal), and monitored for post-sedation side effects indicative of compromised gastrointestinal function, such as decreased appetite, cessation of defecation or abdominal distension.

Descriptive statistics (presented as mean ± standard deviation) were derived for all measured parameters and Mann Whitney tests were conducted at a 95% confidence level to assess the differences between the two protocols (IBM SPSS Statistics for Windows Version 21.0, IBM Corporation, Armonk, New York 10504, USA).

## RESULTS

All animals in this study demonstrated standing sedation, and no supplemental drugs were necessary to complete the examinations and procedures (reproductive evaluation, blood collection and ophthalmic examination without ophthalmoscopy). There was no difference between the times from injection to mild sedation between the two protocols (Table 2). BA tended to produce moderate sedation faster than BD, however there was no significant difference in this study. The BD combination produced more profound sedation, with all animals reaching a moderate level of sedation and leaning on the bars with their head lowered to the ground. They showed minimal ear movement when manipulated and showed no response to potentially mildly noxious procedures, such as phlebotomy. Sedation was consistent in the BD animals and reduced in depth only when antagonists were administered. In the BA group, all four animals reached mild sedation with two achieving moderate sedation, but all animals showed responses such as ear twitching and spontaneous head elevation when manipulated. BA animals remained relatively responsive throughout the procedure and although ocular examination was possible, the rhinoceroses reacted by demonstrating blepharospasm and head movement. Time to full antagonism varied between protocols (*P* = 0.034): animals given BD took longer (132.3 ± 17.2 min) to show normal mentation and ambulation following antagonism, compared with BA (7.5 ± 2.5 min). However, two

**Table 3.** Summary of physiological parameters measured during standing sedation.<sup>a</sup>

Physiological parameter measured	Butorphanol/detomidine	Butorphanol/azaperone	<i>P</i> value from paired <i>t</i> -test
Rectal temperature (°F)	96.9 ± 0.5 (4, 7)	98.7 ± 0.35 (3, 7)	0.034
Mean heart rate (beats/min)	42.5 ± 2.9 (5, 12)	54.2 ± 10.3 (3, 9)	0.091
Mean respiration rate (breaths/min)	7.1 ± 2.4 (5, 14)	10 ± 2 (1, 2)	—
Mean oxygen saturation of hemoglobin (%)	91.1 ± 0.3 (3, 8)	91 (1, 1)	—
Mean systolic arterial pressure (mmHg)	151.8 ± 6.5 (3, 6)	77.5 ± 13.3 (4, 12)	0.032
Mean diastolic arterial pressure (mmHg)	98.4 ± 33.0 (3, 6)	50.9 ± 9.22 (4, 12)	0.034
Mean arterial pressure (mmHg)	123.9 ± 25.4 (3, 6)	57.9 ± 11.4 (4, 12)	0.157

<sup>a</sup> Mean ± standard deviation. (*n*<sup>1</sup>, *n*<sup>2</sup>) = number of animals, total number of measurements from included animals.

of the four animals (Rhino ID 2 and 4) given the BA combination demonstrated no signs of sedation at antagonism, indicating that this combination produces a shorter duration of sedation (<22.3 ± 2.9 min). Antagonists were administered irrespective of the level of sedation at the end of the procedure to prevent gastrointestinal side effects, which are reported with the use of both butorphanol and detomidine in equids.

Mean rectal temperature, indirect systolic pressure and indirect diastolic pressure differed between the two protocols (Table 3). Mean heart rate and indirect diastolic pressure did not differ between the protocols. Mean respiration rate and oxygen saturation were not compared statistically due to insufficient data.

Venous blood gas results for animals sedated with BA and BD are listed in Table 4, with no statistically significant differences between the two protocols. Blood collection occurred at similar times following induction during both protocols (BA 9.2 ± 2.5 min, BD 9.8 ± 1.5 min). Neither of the protocols resulted in significant changes in blood pH when compared with both unsedated equine reference ranges and with retrospective

venous blood gas values from conscious white rhinoceroses (*n* = 4; Cracknell, unpubl. data).<sup>34</sup> PvCO<sub>2</sub> was higher in both BA and BD than reported equine ranges, with BD having a higher PvCO<sub>2</sub> than BA. However, no significant changes were noted when compared to white rhinoceros reference ranges. Venous blood gas analysis showed that BD protocol produced a lower mean PvO<sub>2</sub> (35.0 ± 4.4 mmHg) and a reduced arterial oxygen saturation of hemoglobin (SpO<sub>2</sub>) (62.0 ± 9.6%) compared to the BA protocol. Base excess, bicarbonate and total carbon dioxide levels measured during both protocols were elevated when compared with horses.

No gastrointestinal side effects were noted during the recovery period. Once released from the chute animals ate hay immediately, and although some individuals continued to show slight sedation during the recovery period (BD protocol, animals 2, 4, and 5), no behavioral problems were noted when introduced to stall mates.

## DISCUSSION

This study utilized two different sedation protocols with doses selected based on reports

**Table 4.** Summary of venous blood gas analysis results.<sup>a</sup>

	Butorphanol/ detomidine ( <i>n</i> = 4)	Butorphanol/ azaperone ( <i>n</i> = 4)	<i>P</i> value from paired <i>t</i> -test	Conscious equine venous blood gas ( <i>n</i> = 22) <sup>35</sup>	Conscious <i>Ceratotherium simum</i> venous blood gas ( <i>n</i> = 4; Cracknell, unpubl. data)
pH	7.4 ± 0.0	7.4 ± 0.0	0.149	7.41 ± 0.03	7.34 ± 0.04
PvCO <sub>2</sub> (mmHg)	60.5 ± 4.8	54.0 ± 3.2	0.057	45.14 ± 3.17	60.1 ± 6.69
PvO <sub>2</sub> (mmHg)	35.0 ± 4.4	45.3 ± 6.4	0.057	38.05 ± 6.02	51.4 ± 11.6
BE (mmol/L)	8.8 ± 2.9	8.5 ± 2.9	0.557	4.23 ± 3.35	—
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	34.2 ± 2.1	33.2 ± 2.7	0.773	28.86 ± 2.90	—
tCO <sub>2</sub> (mmol/L)	36.3 ± 2.3	34.8 ± 2.5	0.554	30.14 ± 3.06	—
SO <sub>2</sub> (%)	62.0 ± 9.6	78.8 ± 6.9	0.057	71.05 ± 7.57	—

<sup>a</sup> Mean ± standard deviation. (*n*) = number of animals that contributed a venous blood sample for analysis.

published in greater one-horned rhinoceroses and in other rhinoceros species, in combination with 'pilot study' sedations performed at the authors' institution. The BD combination produced reliable and profound sedation in every individual. Animals in this group showed minimal response to manipulation and the depth of sedation was only reduced with the administration of antagonists. In contrast, BA consistently induced mild sedation with half of the animals achieving moderate sedation. Anxious animals were more alert using this combination, although sedation sufficient for venipuncture was produced in all animals. The adult male was given higher doses of both butorphanol and azaperone due to his age and sex class, and this produced the most reliable moderate sedation in the BA group. Based on estimated weights, the BA sedative dose was 0.06 mg/kg of both butorphanol and azaperone in the male, and 0.05 mg/kg of both drugs in the females, suggesting that the increased dosage produces more reliable moderate sedation in this species.

The BA protocol resulted in moderate sedation within five minutes, although only half of the animals reached this level of sedation. This combination also resulted in a shorter duration of sedation, with animals decreased or no sedation at the time of reversal ( $22.3 \pm 2.9$  min). This is beneficial for short procedures, such as venipuncture and non-invasive treatments, but cannot be recommended for more invasive procedures or those greater than 20 min in duration. In contrast, the BD combination resulted in mild sedation with similar induction times to BA and consistently achieved moderate sedation in all five individuals. The BD protocol produced significantly longer times to full antagonism ( $132.3 \pm 17.2$  min). This protocol may not be suitable if immediate alertness, normal mentation, and ambulation are required immediately following a procedure. Alternative doses of antagonists used may reduce the recovery time.

All physiological measurement readings were taken over the period of sedation, from the onset of mild sedation to antagonism. These times were similar for both protocols; BD measurements were taken from nine to 26 min after induction, and from seven to 22 min after induction during BA. Rectal temperatures were noted to be significantly different between the two protocols, and the lower temperature seen with BD is likely a result of early peripheral vasoconstriction, including within the rectal mucosa.<sup>30,36</sup> Ambient temperatures within the barn were consistent

between studies. Differences in environmental temperature were considered as a possible cause for the difference seen in rectal temperatures, although this is unlikely given that barns are heated during winter months. The mean heart rates noted using both protocols were reduced when compared to ranges published for etorphine-anesthetized greater one-horned rhinoceroses (60–80 beats/min).<sup>2,22,24</sup> Increased heart rates are expected during etorphine anesthesia due to increased sympathetic tone exacerbated by hypoxemia.<sup>15,17,23,24</sup> No reference ranges are published for conscious heart rates in greater one-horned rhinoceroses; however, the mean heart rates observed in both protocols were slightly higher than those seen in conscious white rhinoceroses ( $39 \pm 0.8$  beats/min).<sup>6</sup> Heart rate may have been higher during the BA procedures ( $54.2 \pm 10.3$  beats/min) because of the observed increased responsiveness.

Mean systolic and diastolic pressures were different between the protocols ( $P < 0.05$ ), with BD sedation resulting in values similar to values reported in conscious, unrestrained white rhinoceroses.<sup>6</sup> This was surprising as the BD group was expected to have had mild hypertension due to peripheral vasoconstriction. However, it is possible that this early phase was missed and noninvasive indirect blood pressure monitoring was achieved in the second phase of centrally mediated cardiovascular changes.<sup>33,36</sup> Hypotension noted during BA sedation was presumed to be associated with peripheral-mediated cardiovascular depression and vasodilation associated with azaperone use. There is evidence that azaperone reduces mean arterial pressures when used in conjunction with etorphine in white rhinoceroses.<sup>15</sup> It has also been reported to cause a reduction in mean arterial pressure of 30–38% when given to domestic equids, with peak effect occurring within ten minutes and lasting for over four hours, well after the sedative action has disappeared.<sup>29</sup> The previous reported use of BA combinations in other rhinoceros species did not report blood pressures.<sup>39,48</sup> Due to the hypotension reported here, blood pressure monitoring is recommended if this protocol is to be utilized in greater one-horned rhinoceroses. Consideration should be given to the lack of cardiovascular reference ranges in normal, unsedated greater one-horned rhinoceroses.<sup>35</sup>

While there are several reports of arterial blood gas analysis in both conscious and anesthetized rhinoceroses, there are no published reference ranges for venous blood gases in any rhinoceros

species.<sup>6,15,17,28,48</sup> Both protocols resulted in similar pH ( $7.4 \pm 0.0$ ), which was comparable to normal unsedated equine venous samples,<sup>34</sup> and that of mechanically ventilated greater one-horned rhinoceroses under anesthesia.<sup>22</sup> However, animals in this study were mildly alkalemic when compared to conscious white rhinoceroses ( $n = 4$ ; Cracknell, unpubl. data). Other venous blood gas values found for the rhinoceroses in this study fall outside the range described for the horse.<sup>33,34</sup> When compared to values found in conscious, unrestrained white rhinoceroses ( $n = 4$ ; Cracknell, unpubl. data), BD produced lower PvO<sub>2</sub> and elevated PvCO<sub>2</sub>, and BA produced elevated PvO<sub>2</sub> and elevated PvCO<sub>2</sub>, although these deviations were not considered to be significant. PvCO<sub>2</sub> was higher in BD than BA, both being higher than reported equine ranges but similar to unsedated white rhinoceroses PvCO<sub>2</sub> (Cracknell, unpubl. data). This may be a result of the hypotension seen with the BA protocol leading to reduced cardiac output and tissue perfusion. PvO<sub>2</sub> values were lower in BD animals than BA. Since observed respiratory rates fall within normal ranges for both conscious and anesthetized rhinoceroses (6–12 breaths/min),<sup>31,35</sup> the reduced PvO<sub>2</sub> likely represents detomidine-associated transient reduced cardiac output and/or impaired pulmonary gas exchange due to pulmonary vasoconstriction. This is supported by the lower heart rate seen with BD and is similar to that seen in domestic horses administered BD.<sup>33</sup> Both protocols resulted in SpO<sub>2</sub> of 91%. Comparison of the calculated SO<sub>2</sub> from the venous blood gas analysis supports both the pulmonary compromise in the BD and the reduced tissue perfusion seen in the BA group. Consequently, supplementary oxygen is recommended for rhinoceroses under both sedative combinations. Intranasal insufflation or a facemask over the nostrils have been found to be tolerated in conscious rhinoceroses in a restraint chute, and is therefore likely to be well tolerated in both sedative groups.<sup>32</sup>

Butorphanol and detomidine were antagonized using naltrexone and tolazoline respectively at doses listed in Table 1. Antagonists were administered intramuscularly for consistency. Tolazoline, a nonselective  $\alpha$ -receptor antagonist, is licensed for equine use in the United States to reverse the effects of  $\alpha$ -2 agonists, and is effective in reversing the cardiovascular and gastrointestinal side effects of xylazine in ruminants.<sup>19,30</sup> Intravenous administration of tolazoline has been noted to incompletely antagonize the effect of detomidine in horses, although the time to

recovery was shortened.<sup>19</sup> A reduction in the depth of sedation was noted  $5.0 \pm 1.4$  min following the administration of tolazoline in this study at a dose of approximately 1 mg/kg i.m. Horses have been given tolazoline doses of up to 4 mg/kg,<sup>19</sup> and increasing the dose from 1 mg/kg to 4 mg/kg may further decrease the recovery time in BD rhinoceroses. Although atipamezole is a more specific  $\alpha$ -2 antagonist and has been found to have 100 times stronger affinity to central nervous system  $\alpha$ -2 receptors,<sup>30,44</sup> it has been reported to have less efficacy in antagonizing detomidine in horses when compared to tolazoline.<sup>19</sup> In addition, the increased cost of atipamezole compared to tolazoline does not support the use of this alternative antagonist. Butorphanol was antagonized with naltrexone, at five times the butorphanol dose in the BD group and twice the butorphanol dose in the BA group, except for one individual, which received five times the dose. This dose was determined by the level of sedation being demonstrated at the time of antagonism and did not affect recovery time. Both doses are within the published reference range of naltrexone for the antagonism of butorphanol in rhinoceroses (one to five times the dose of butorphanol).<sup>40</sup> Therefore, both protocols are viable options for the sedation of healthy captive greater one-horned rhinoceroses with both protocols providing the opportunity to partially or completely antagonize the sedative agents using intramuscularly administered agents.

## CONCLUSION

BD and BA combinations were used successfully to produce reliable mild to moderate sedation in minimally trained rhinoceroses, in order to perform minimally invasive procedures such as ophthalmic examinations and phlebotomy. Doses used appeared appropriate for inducing standing sedation based on the animals' response in the chute and recumbency was not induced. BD resulted in more consistent and reliable sedation. However, mild cardiopulmonary compromise was documented with slightly increased PvCO<sub>2</sub> and decreased PvO<sub>2</sub>. In addition, time to full reversal after the administration of antagonists was prolonged, which was considered to be as a result of the partial antagonism of detomidine. BA produced moderate sedation in only half of the animals; all animals remained relatively responsive throughout the procedure. Profound hypotension was noted in the BA group and it should be used cautiously in individuals with compromised health or cardiovascular function. No



gastrointestinal side effects were noted with the use of either combination.

*Acknowledgments:* The authors would like to thank Lana Kelly (RVT) and the Animal Management staff at the Wilds for their assistance and support of this study, and Dr. Alex Dugdale, University of Liverpool for reviewing this manuscript. Funding was provided in part by the Conservation and Collection Management Committee, Columbus Zoo and Aquarium.

### LITERATURE CITED

- Atkinson, M. W., B. Hull, A. R. Gandolf, and E. S. Blumer. 2001. Long-term medical and surgical management of chornic pododermatitis in a greater one-horned rhinoceros (*Rhinoceros unicornis*): a progress report. *In: Schwammer, H. M., T. J. Foose, M. Fouraker, and D. Olson, (eds.). Proceedings of the International Elephant and Rhino Research Symposium, Vienna. Pp. 159–163.*
- Atkinson, M. W., B. Hull, A. R. Gandolf, and E. S. Blumer. 2002. Repeated chemical immobilization of a captive greater one-horned rhinoceros (*Rhinoceros unicornis*), using combinations of etorphine, detomidine, and ketamine. *J. Zoo Wildl. Med. 33: 157–162.*
- Bertelsen, M. F., R. A. Olberg, K. G. Mehren, D. A. Smith, and G. J. Crawshaw. 2004. Surgical management of rectal prolapse in an Indian rhinoceros (*Rhinoceros unicornis*). *J. Zoo Wildl. Med. 35: 245–247.*
- Blane, G. F., A. L. Boura, A. E. Fitzgerald, and R. E. Lister. 1967. Actions of etorphine hydrochloride, (M99): a potent morphine-like agent. *Br. J. Pharmacol. Chemother. 30: 11–22.*
- Blumer, E. 1996. Restraint and anesthesia. *In: Fouraker, M., and T. Wagener (eds.). AZA Rhinoceros Husbandry Resource Manual, Cockrell Printing Company, Fort Worth Zoological Park, Fort Worth, Texas. Pp. 46–51.*
- Citino, S. B., and M. Bush. 2007. Reference cardiopulmonary physiologic parameters for standing, unrestrained white rhinoceroses (*Ceratotherium simum*). *J. Zoo Wildl. Med. 38: 375–379.*
- Clarke, K. W., and B. S. Paton. 1988. Combined use of detomidine with opiates in the horse. *Equine Vet. J. 20: 331–334.*
- Dodman, N. H., and A. E. Waterman. 1979. Paradoxical excitement following the intravenous administration of azaperone in the horse. *Equine Vet. J. 11: 33–35.*
- Esson, D. W., J. F. Wellehan, M. Lafortune, A. Valverde, and S. B. Citino. 2006. Surgical management of a malacic corneal ulcer in a greater one-horned Asian rhinoceros (*Rhinoceros unicornis*) using a free island tarsoconjunctival graft. *Vet. Ophthalmol. 9: 65–69.*
- Fouraker, M., and T. Wagener. 1996. AZA Rhinoceros Husbandry Resource Manual. Cockrell Printing Company, Fort Worth Zoological Park, Fort Worth, Texas.
- Gandolf, A. R., A. M. Willis, E. S. Blumer, and M. W. Atkinson. 2000. Melting corneal ulcer management in a greater one-horned rhinoceros (*Rhinoceros unicornis*). *J. Zoo Wildl. Med. 31: 112–117.*
- Gandolf, A. R., T. M. Wolf, and R. W. Radcliffe. 2006. Serial chemical restraint for treatment of decubitus ulcers in two neonatal white rhinoceroses (*Ceratotherium simum*). *J. Zoo Wildl. Med. 37: 387–392.*
- Harthoorn, A.M. 1973. Review of wildlife capture drugs in common use. *In: E. Young (ed.). The Capture and Care of Wild Animals. Human & Rousseau Publishers, Cape Town. Pp. 14–34.*
- Harthoorn, A. M. 1976. The chemical restraint of the principal groups of wild and captive animals. *In: Harthoorn, A. M. (ed.). The Chemical Capture of Animals. Bailliere Tindall, London. Pp. 192–224.*
- Hattingh, J., C. M. Knox, and J. P. Raath. 1994. Arterial blood pressure and blood gas composition of white rhinoceroses under etorphine anesthesia. *S. Afr. J. Wildl. Res. 24: 12–14.*
- Haymerle, A., A. Fahlman, and C. Walzer. 2010. Human exposures to immobilising agents: results of an online survey. *Vet. Rec. 167: 327–332.*
- Heard, D. J., J. H. Olsen, and J. Stover. 1992. Cardiopulmonary changes associated with chemical immobilization and recumbency in a white rhinoceros (*Ceratotherium simum*). *J. Zoo Wildl. Med. 23: 197–200.*
- Holden, M. D., J. Gregory, V. Watkins, and L. Radford. 2006. Operant-conditioning programme for white rhinoceros, black rhinoceros and Indian or greater one-horned Asian rhinoceros. *Int. Zoo Yearb. 40: 144–149.*
- Hubbell, J. A., and W. W. Muir. 2006. Antagonism of detomidine sedation in the horse using intravenous tolazoline or atipamezole. *Equine Vet. J. 38: 238–241.*
- Hubbell, J. A. 2009. Anxiolytics, non-opioid sedative-anxiolytics, and opioid analgesics. *In: Hubbell, J. A., and W. W. Muir (eds.). Equine Anesthesia, Monitoring and Emergency Therapy, 2nd ed. Saunders Elsevier, St. Louis. Pp. 185–209.*
- King, J. M. 1969. The capture and translocation of the black rhinoceros. *E. Afr. Wildl. J. 7: 115–130.*
- Klein, L. V., R. A. Cook, P. P. Calle, B. L. Raphael, P. Thomas, M. D. Stetter, W. J. Donawick, and J. J. Foerner. 1997. Etorphine-Isflurane-oxygen anesthesia for ovariohysterectomy in an Indian rhinoceros (*Rhinoceros unicornis*). *Proc. Am. Assoc. Zoo. Vet. 127–130.*
- Kock, M. D., P. v. Morkel, M. W. Atkinson, and C. Foggin. 1995. Chemical immobilization of free-ranging white rhinoceros (*Ceratotherium simum simum*) in Hwange and Matobo National Parks, Zimbabwe, using combinations of etorphine (M99), fentanyl, xylazine and detomidine. *J. Zoo Wildl. Med. 26: 207–219.*
- Kock, R. A., and P. C. Pearce. 1985. Anaesthesia in zoo ungulates. *Vet. Anaes. Anal. 13: 59–88.*

25. Kohn, C. W., and W. W. Muir. 1988. Selected aspects of the clinical pharmacology of visceral analgesics and gut motility modifying drugs in the horse. *J. Vet. Intern. Med.* 2: 85–91.
26. Kreeger, T. J., and J. M. Arnemo. 2007. *Handbook of Wildlife Chemical Immobilization*. Sunquest Publishing, Shanghai.
27. Lamont, L. A., and K. A. Mathews. 2007. Opioids, non-steroidal anti-inflammatories, and analgesic adjuvants. *In: Tranquilli, W. J., J. C. Thurmon, and K. A. Grimm (eds.). Lumb and Jones' Veterinary Anesthesia and Analgesia*. Blackwell Publishing, Iowa. Pp. 241–271.
28. LeBlanc, P. H., S. W. Eicker, M. Curtis, and B. Beehler. 1987. Hypertension following etorphine anesthesia in a rhinoceros (*Diceros simus*). *J. Zoo Wildl. Med.* 18: 141–143.
29. Lees, P., and L. Serrano. 1976. Effects of azaperone on cardiovascular and respiratory functions in the horse. *Br. J. Pharmacol.* 56: 263–269.
30. Lemke, K. A. 2007. Anticholinergics and sedatives. *In: Tranquilli, W. J., J. C. Thurmon, and K. A. Grimm (eds.). Lumb and Jones' Veterinary Anesthesia and Analgesia*. Blackwell Publishing, Iowa. Pp. 203–239.
31. Miller, R. E. 2003. Rhinocerotidae (Rhinoceroses). *In: Fowler, M. E., and R. E. Miller (eds.). Zoo and Wild Animal Medicine*, 5th ed. Saunders, St. Louis. Pp. 558–569.
32. Morkel, P. v., R. W. Radcliffe, M. Jago, P. du Preez, M. J. F. Flaminio, D. V. Nydam, A. Taft, D. Lain, M. M. Miller, and R. D. Gleed. 2010. Acid-base balance and ventilation during sternal and lateral recumbency in field immobilized black rhinoceros (*Diceros bicornis*) receiving oxygen insufflation: a preliminary report. *J. Wildl. Dis.* 46: 236–245.
33. Nyman, G., S. Marntell, A. Edner, P. Funkquist, K. Morgan, and G. Hedenstierna. 2009. Effect of sedation with detomidine and butorphanol on pulmonary gas exchange in the horse. *Acta Vet. Scand.* 51: 22.
34. Peiro, J. R., A. S. Borges, R. C. Goncalves, and L. C. Mendes. 2010. Evaluation of a portable clinical analyzer for the determination of blood gas partial pressures, electrolyte concentrations, and hematocrit in venous blood samples collected from cattle, horses, and sheep. *Am. J. Vet. Res.* 71: 515–521.
35. Portas, T. J. 2004. A review of drugs and techniques used for sedation and anaesthesia in captive rhinoceros species. *Aust. Vet. J.* 82: 542–549.
36. Posner, L. P., and P. Burns. 2009. Sedative agents: tranquilizers, alpha-2-agonists, and related agents. *In: Riviere, J. E., and M. G. Papich (eds.). Veterinary Pharmacology & Therapeutics*. Wiley-Blackwell, Iowa. Pp. 337–380.
37. Raath, J. P. 1999. Anesthesia of white rhinoceros. *In: Fowler, M. E., and R. E. Miller (eds.). Zoo & Wild Animal Medicine: Current Therapy*, 4th ed. W. B. Saunders Co., Philadelphia. Pp. 556–561.
38. Radcliffe, R. M., D. A. Hendrickson, G. L. Richardson, J. R. Zuba, and R. W. Radcliffe. 2000. Standing laparoscopic-guided uterine biopsy in a southern white rhinoceros (*Ceratotherium simum simum*). *J. Zoo Wildl. Med.* 31: 201–207.
39. Radcliffe, R. W., S. T. Ferrell, and S. E. Childs. 2000. Butorphanol and azaperone as a safe alternative for repeated chemical restraint in captive white rhinoceros (*Ceratotherium simum*). *J. Zoo Wildl. Med.* 31: 196–200.
40. Radcliffe, R. W., and P. v. Morkel. 2007. Rhinoceroses. *In: West, G., D. J. Heard, and N. Caulkett (eds.). Zoo Animal and Wildlife Immobilization and Anesthesia*. Blackwell Publishing, Iowa. Pp. 543–566.
41. Reuter, H. O., and H. Winterbach. 1998. Current capture techniques and drug dosage regime for the immobilization and tranquilization of free-ranging black rhinoceros (*Diceros bicornis bicornis*) in Namibia. *Proc. Am. Assoc. Zoo. Vet. and Am. Assoc. Wildl. Vet. Joint Conference*. 1998: 410–415.
42. Roth, T. L., M. A. Stoops, M. W. Atkinson, E. S. Blumer, M. K. Campbell, K. N. Cameron, S. B. Citino, and A. K. Maas. 2005. Semen collection in rhinoceroses (*Rhinoceros unicornis*, *Diceros bicornis*, *Ceratotherium simum*) by electroejaculation with a uniquely designed probe. *J. Zoo Wildl. Med.* 36: 617–627.
43. Schmitt, D., J. Bradford, and D. A. Hardy. 1996. Azaperone for standing sedation in Asian elephants (*Elephas maximus*). *Proc. Am. Assoc. Zoo. Vet. Annu. Meet.* 1996: 48–51.
44. Schwartz, D. D., and T. P. Clark. 1998. Selectivity of atipamezole, yohimbine and tolazoline for alpha-2 adrenergic receptor subtypes: implications for clinical reversal of alpha-2 adrenergic receptor mediated sedation in sheep. *J. Vet. Pharmacol. Ther.* 21: 342–347.
45. Sutton, D. G., T. Preston, R. M. Christley, N. D. Cohen, S. Love, and A. J. Roussel. 2002. The effects of xylazine, detomidine, acepromazine and butorphanol on equine solid phase gastric emptying rate. *Equine Vet. J.* 34: 486–492.
46. von Houwald, F. 2002. Health. *In: Guldenschuh, G., and F. von Houwald (eds.). Husbandry Manual for the Greater One-horned or Indian Rhinoceros (*Rhinoceros unicornis*)*. Basel Zoo, Basel. Pp. 36–55.
47. von Houwald, F. F. 2001. Foot Problems in Indian Rhinoceroses (*Rhinoceros unicornis*) in Zoological Gardens: Macroscopic and Microscopic Anatomy, Pathology, and Evaluation of the Causes. University of Zurich, Zurich.
48. Wenger, S., W. Boardman, P. Buss, D. Govender, and C. Foggin. 2007. The cardiopulmonary effects of etorphine, azaperone, detomidine, and butorphanol in field-anesthetized white rhinoceroses (*Ceratotherium simum*). *J. Zoo Wildl. Med.* 38: 380–387.

Received for publication 7 April 2013