

EVALUATION OF ETORPHINE AND MIDAZOLAM ANESTHESIA, AND THE EFFECT OF INTRAVENOUS BUTORPHANOL ON CARDIOPULMONARY PARAMETERS IN GAME-RANCHED WHITE RHINOCEROSSES (*CERATOTHERIUM SIMUM*)

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Abstract: Nineteen white rhinoceroses (*Ceratotherium simum*) were anesthetized with 4 mg of etorphine hydrochloride; 35–40 mg of midazolam; and 7,500 international units of hyaluronidase for dehorning purposes at a game ranch in South Africa, to investigate this anesthetic combination. Median time to recumbency was 548 sec (range 361–787 sec). Good muscle relaxation and no muscle rigidity or tremors were observed in 18 animals, and only 1 individual showed slight tremors. In addition, all animals received butorphanol i.v. 5 min after recumbency at the ratio of 10 mg of butorphanol per 1 mg of etorphine. Blood gas and selected physiologic parameters were measured in the recumbent animal, immediately before and 10 min after the administration of butorphanol. Statistically significant improvements were observed in blood gas physiologic and cardiopulmonary parameters 10 min after the administration of butorphanol, with a reduction in arterial partial pressure of carbon dioxide, systolic blood pressure, and heart rate and an increase in pH, arterial partial pressure of oxygen, oxygen saturation, and respiratory rate (all $P < 0.005$). After i.v. naltrexone reversal, recovery was uneventful, and median time to walking or running was 110 sec (range 71–247 sec). The results indicate etorphine and midazolam combination is an effective alternative anesthetic protocol and produces good muscle relaxation. Furthermore, i.v. butorphanol was associated with improved blood gas values and cardiopulmonary function for at least 10 min postinjection.

Key words: Blood gas values, butorphanol, *Ceratotherium simum*, etorphine, midazolam, white rhinoceros.

INTRODUCTION

A safe and effective anesthesia is necessary for handling and transporting the threatened southern white rhinoceroses (*Ceratotherium simum*).^{5,7} In captive rhinoceroses, butorphanol with medetomidine or azaperone provides adequate and safe standing sedation.^{1,23,26} In free-ranging white rhinoceroses however, etorphine remains the primary agent of choice because of its high concentration and rapid induction.^{5,25,27} The effect of etorphine starts within 2–12 min and peaks around 20–30 min after administration.²³ Azaperone is frequently used in combination with etorphine to partially negate hypertension secondary to increased cardiac output and increased peripheral vascular resistance.^{14,15,25} However, rhinoceroses anesthetized

with etorphine and azaperone still develop adverse physiologic changes including hypoxia, hypercapnia, acidosis, tachycardia, muscle rigidity, and tremors.^{5,12,27} When recumbent, the large body mass of white rhinoceroses adds pressure to their dependent anatomy, thereby reducing oxygen supply and peripheral blood circulation. Etorphine-associated muscular tremors and hypertonicity contribute to an increased body temperature and a buildup of lactic acid in muscles.⁵ Therefore, capture myopathy is common in recumbent white rhinoceroses.^{5,27}

The effect of additional oxygen supplied to anesthetized white rhinoceroses has been investigated in an attempt to minimize hypoxemia and prevent capture myopathy.^{8,13} Nasotracheal oxygen insufflation alone was found to improve hemoglobin oxygenation on recumbent white rhinoceroses;⁸ when combined with a single i.v. dose of 15 mg of butorphanol per milligram of etorphine, it improved the etorphine-induced hypoxemia, but did not completely reverse all components of respiratory depression.¹³

In addition to investigating methods to improve oxygenation, it is necessary to evaluate alternative tranquilizers in combination with etorphine, which may enhance muscle relaxation. Benzodi-

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azepines, including diazepam, midazolam, and zolazepam, are centrally acting muscle relaxants that reduce muscle spasms and spasticity²² and can be used to treat capture myopathy.²¹ Midazolam, an imidazobenzodiazepine, has unique solubility characteristics and therefore has a rapid onset of action.²⁰ It is metabolized in the liver, and the half-life and duration of activity are shorter than those of diazepam.²² Midazolam is more potent than diazepam, has a profound amnesiac effect, and has been used orally to bait large carnivores.¹⁶ In addition, its excellent muscle relaxation properties improve deep ventilation. This may counteract oxygen depletion caused by muscle tremors and hyperthermia inherent with the use of opioids.²⁷ Furthermore, the calming effect and minimal cardiopulmonary effects of midazolam in domestic animals²⁰ are promising for its use in wildlife medicine. Midazolam has been used previously to help maintain anesthesia in a white rhinoceros;²⁴ and in combination with etorphine and butorphanol in a dart, it improved cardiopulmonary parameters in white rhinoceroses, but not all animals in the study became recumbent.^{6,7} The cardiopulmonary profiles of white rhinoceroses anesthetized with etorphine and midazolam alone have not been reported.

Butorphanol tartrate, a μ -receptor antagonist and κ -receptor agonist,⁴ has been used alone or in combination with azaperone to sedate or anesthetize rhinoceros species.^{5,7,23,26} In previous studies, the effect of butorphanol on cardiopulmonary parameters in rhinoceroses anesthetized with etorphine and azaperone were investigated.^{3,9,18,30} Various studies found substantial improvements in cardiopulmonary parameters in white rhinoceroses anesthetized with etorphine and azaperone when butorphanol was administered at the ratio of 10 mg of butorphanol per milligram of etorphine, i.v. after initial blood collection, but tremors and muscle rigidity were present.^{3,9} Ear twitching, limb rigidity and muscle tremors were observed in all study animals.^{3,9}

This study evaluated etorphine and midazolam as an anesthetic regime in game-ranched white rhinoceroses and assessed the effect of i.v. butorphanol, administered at a ratio of 10 mg of butorphanol per 1 mg of etorphine on the cardiopulmonary parameters of the recumbent, anesthetized white rhinoceroses.

MATERIALS AND METHODS

The study animals were 19 adult game-ranched white rhinoceroses, 10 females and 9 males, in good condition. They were anesthetized in No-

vember 2012 at a private game farm in the Northern West Province, South Africa (26°86'S, 26°66'E, 1,333 m above sea level) for dehorning, identification, and translocation purposes. Each animal was identified from a distance by the specific ear notches according to an individual numbering system. Their estimated weights ranged between 1,600 and 1,900 kg. The study subjects were darted from a vehicle into the quadriceps musculature or neck with 4 mg of etorphine hydrochloride (Captivon, Wildlife Pharmaceuticals, White River 1240, South Africa; 9.8 mg/ml), 35–40 mg of midazolam (midazolam hydrochloride, Kyron Laboratories, Benrose 2094, South Africa; 50 mg/ml), and 7,500 international units of hyaluronidase (Hyalase, Kyron Laboratories) in metal darts equipped with a 62.5-mm length, 2.41-mm gauge barbed needle (Type P Pneu-darts, Pneu-dart, Inc., Williamsport, Pennsylvania, USA). The darts were fired from a gas powered projector (X-Caliber, Pneu-dart, Inc., Williamsport, Pennsylvania 17701, USA). For each animal, the time from darting time to recumbency was recorded in seconds. The position when recumbent (lateral or sternal) was also noted. A blindfold was applied once the anesthesia was deep enough to approach safely. Stationary, heavily sedated animals were roped down by applying a rope around a leg and pushing the body to the same side to expedite the procedure. After the initial assessment, an i.v. catheter (Jelco I.V. Catheter Radiopaque, Smiths Medical, Croydon 1619, South Africa; 40-mm length, 1.27-mm gauge) was inserted into the auricular vein, and then ear plugs were inserted. The dart was removed, and then the dart wound was injected with 10 ml of an injectable penicillin mixture (150 mg/ml procaine penicillin and 112.5 mg/ml benzathine penicillin, Lentrax, Merial, Midrand, 1685, South Africa).

A pulse oximeter sensor (Veterinary pulse oximeter, H100B, Edan Diagnostics, San Diego, California 92121, USA) was placed on a scarified edge of the pinna to measure the heart rate and hemoglobin oxygen saturation. The heart rate was also measured by auscultation, and the rectal temperature was measured and recorded. Visual assessment of thoracic and abdominal excursions and air movement at the nares were used to record the respiration rate. A self-inflating human wrist blood pressure monitor (Visocor HM40, Uebe Medical GmbH, 97877 Wertheim, Germany) attached to the tail at the level of the heart was used to measure changes in systolic and diastolic blood pressure. In 15 study animals, arterial blood was

collected into 1-ml heparinized syringes from the auricular artery at 5 min ($t = 5$) and 15 min ($t = 15$) after the animal had become recumbent ($t = 0$). Arterial partial pressure of carbon dioxide (PaCO_2), arterial partial pressure of oxygen (PaO_2), pH, sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), glucose, and lactate were measured immediately using a portable epoc[®] Host blood gas analyzer (Epocal, Inc., Ottawa, Ontario K1G 3P5, Canada) with epoc BGEM test cards ($n = 15$). Hematocrit, calculated hemoglobin and bicarbonate (cHCO_3^-), base excess, arterial hemoglobin oxygen saturation (cSaO_2), and the concentration of total carbon dioxide were calculated simultaneously by the same machine. Blood gas values were not corrected for patient temperature and are representative of the analyzers default temperature of 37°C. Body position was noted at $t = 5$ and $t = 15$, and the level of anesthesia and relaxation and the presence or absence of ear twitching, muscle tremors, and leg movements were recorded.

Immediately after the first arterial blood was collected ($t = 5$), butorphanol tartrate (Butonil, Wildlife Pharmaceuticals; 50 mg/ml) was injected i.v. at the ratio of 10 mg/1 mg of etorphine into the auricular vein.

Once all procedures were completed, 20 mg of naltrexone (Trexonil, Wildlife Pharmaceuticals; 50 mg/ml) per 1 mg of etorphine was injected i.v. to antagonize the opioid component of the anesthesia. The blindfold, i.v. catheter, and ear-plugs were removed. The time from injection of the antagonist to standing was recorded in seconds. The rhinoceroses were observed from a distance by rangers for the rest of the day.

Physiologic and blood gas parameters before and after i.v. butorphanol were compared using a t -test (i.e., the difference between $t = 5$ and $t = 15$ was tested against no change; nil difference). The assumption of normality was assessed visually and tested using the Shapiro-Wilk test. When a parameter failed the normality test ($P < 0.10$), the Wilcoxon signed-rank test was used instead to compare values before and after butorphanol injection. The potential impact of explanatory variables such as sex, and position on the parameter difference were explored using a t -test without assumption of equal variance. For parameters that failed the normality test (data should be normally distributed when using the t -test), the Wilcoxon rank-sum test was used instead (no assumption of normal distribution is required). The P values were interpreted at the 0.05 significance level. Statistical analyses were conducted using the statistical package STATA

(Stata Statistical Software Release 13.1, Stata Corporation, College Station, Texas 77840, USA).

RESULTS

In total, 19 animals were anesthetized with etorphine, midazolam, and hyaluronidase. No mortality or morbidity occurred during or after anesthesia. Two animals were roped down because they remained standing while heavily sedated. Once recumbent, neither of these animals made any attempt to stand. All animals seemed healthy based on their behavior, field observations, body condition, and subsequent clinical examination. The median time from darting to recumbency in the animals not roped down was 548 sec (range 361–787 sec). Eighteen animals (95%) showed a fully relaxed anesthesia with good muscle relaxation, no limb rigidity, no muscle tremors, and all legs held in a relaxed position when in lateral recumbency. One animal (5%) also showed a relaxed anesthesia with the legs held in a relaxed position in lateral recumbency, but ear twitching, muscle tremors, and movements of the legs were observed occasionally. The mean of the recorded physiologic data and blood gas values at $t = 5$ and $t = 15$ and subsequent mean differences are reported in Table 1. Most physiologic parameters showed a significant change in the recumbent animals, before and after administration of butorphanol. The respiratory rate significantly increased, whereas heart rate, systolic blood pressure, and diastolic blood pressure significantly decreased after the i.v. administration of butorphanol. Blood gas parameters still showed evidence of respiratory acidosis, hypoxemia, and hypercapnia after i.v. butorphanol, but there was a statistically significant improvement in pH, PaO_2 , PaCO_2 , and SaO_2 at $t = 15$ compared to $t = 5$. Lactate concentrations decreased significantly, whereas glucose concentrations increased significantly between sampling points. Ca^{2+} , cHCO_3^- , the concentration of total carbon dioxide, and base excess did not show any significant change. There was a significant improvement in PaCO_2 in males ($n = 8$) in comparison to females ($n = 7$) ($P = 0.0057$) and the TCO_2 at $t = 15$ ($P = 0.0217$). The animals which stayed in sternal recumbency throughout the entire procedure ($n = 9$) had a significant improvement in PaO_2 (+22.2 mm Hg) compared to animals that were moved from either sternal to lateral recumbency or moved from lateral to sternal recumbency during the procedure ($n = 6$) (+10.1 mm Hg) ($P = 0.0032$) (data not shown). Recovery was uneventful for all study

Table 1. Comparison of physiologic data and arterial blood gas values for anesthetized game-ranch white rhinoceroses (*C. simum*) before and after i.v. injection of butorphanol. Animals were anesthetized with a combination of etorphine, midazolam, and hyaluronidase. Physiologic data and blood samples were collected 5 min after recumbency ($t=5$), immediately before butorphanol (10 mg of butorphanol for each 1 mg of etorphine) was injected and 10 min later ($t=15$). Mean blood gas and physiologic reference values previously reported are added for comparison.¹⁰ Mean differences were compared to zero (no difference) by using t -test to assess the impact associated with butorphanol injection, and P values were interpreted at the 0.05 significance level.

Parameter ^a	Mean reference value (minimum–maximum)	n	Mean at $t=5$ (minimum–maximum)	n	Mean at $t=15$ (minimum–maximum)	n	Mean difference (minimum–maximum)	SE	95% confidence interval	P
Physiologic data										
Resp. rate (breaths/min)	19 (16–23)	19	7 (5–12)	19	10 (6–12)	19	2.11 (0–7)	0.47	1.10–3.10	0.0005 ^b
Heart rate (beats/min)	39 (32–42)	19	111 (64–136)	19	65 (48–100)	19	-45 (-68 to -6)	3.91	-53.2–-36.8	0.0000
Rectal temp. (°C)	36.8 (36.6–37.2)	19	36.8 (36.0–37.9)	19	37.1 (36.2–38.1)	19	0.25 (-0.1 to 0.8)	0.05	0.13–0.37	0.0003
SpO ₂ (%)	— ^c	18	96 (90–100)	18	97 (88–100)	18	1.16 (-3 to 10)	0.84	-0.62–2.95	0.3195 ^b
BP systol (mm Hg)	160 (146–183)	17	176 (107–251)	17	143 (79–183)	15	-44 (-141 to 45)	12.8	-72.1–-16.9	0.0038
BP diastol (mm Hg)	104 (88–117)	17	113 (69–183)	17	89 (35–122)	15	-26 (-86 to 20)	8.8	-45.0–-7.2	0.0102
Blood gas data										
pH	7.391 (7.346–7.431)	15	7.247 (7.154–7.287)	15	7.284 (7.231–7.349)	15	0.037 (-0.04 to 0.09)	0.008	0.02–0.06	0.0005
PaCO ₂ (mm Hg)	49.0 (44.4–53.7)	15	72.8 (63.0–81.3)	15	65.3 (52.7–79.4)	15	-7.5 (-18.1 to 2.6)	1.73	-11.2–-3.8	0.0007
PaO ₂ (mm Hg)	98.3 (90.2–108.6)	15	26.9 (17.9–38.3)	15	44.2 (28.5–56.3)	15	17.34 (-4.1 to 36.4)	2.55	11.9–22.8	0.0008 ^b
Na ⁺ (mmol/L)	—	15	127 (117–135)	15	127 (116–135)	15	0 (-9 to 11)	1.60	-3.4–3.4	1.0000
K ⁺ (mmol/L)	—	15	5.2 (4.3–6.6)	15	5.0 (4.3–6.8)	15	-0.22 (-1.6 to 2.3)	0.24	-0.7–0.3	0.3777
Ca ²⁺ (mmol/L)	—	15	1.48 (1.40–1.54)	15	1.48 (1.34–1.70)	15	-0.002 (-0.15 to 0.22)	0.02	-0.05–0.05	0.9323
Lactate (mmol/L)	—	15	2.77 (0.96–8.67)	15	1.99 (0.53–5.51)	15	-0.78 (-3.32 to 0.13)	0.25	-1.30–-0.24	0.0018 ^b
Glucose (mmol/L)	—	15	5.7 (3.8–8.0)	15	7.3 (4.6–10.6)	15	1.62 (0.2–4.7)	0.42	0.71–2.53	0.0019 ^b
cHct (%)	—	15	53 (46–61)	15	50 (43–58)	15	-2.87 (-8.8 to 3.0)	0.74	-4.44–-1.29	0.0016
cHgb (g/L)	—	15	17.9 (15.6–20.7)	15	16.9 (14.6–19.7)	15	-0.99 (-2.5 to 0.9)	0.24	-1.50–-0.47	0.0011
cHCO ₃ ⁻ (mmol/L)	29.3 (27.3–32.2)	15	31.7 (26.7–36.4)	15	30.9 (27.6–34.6)	15	-0.76 (-5.2 to 1.5)	0.48	-1.78–0.26	0.1338
cTCO ₂ (mmol/L)	—	15	33.9 (29.1–38.8)	15	32.9 (29.2–27.0)	15	-1.00 (-5.7 to 1.6)	0.51	-2.10–0.08	0.0686
cBe ECF (mmol/L)	3.5 (1.9–5.9)	15	4.4 (-2.1 to 9.7)	15	4.2 (0.1–7.7)	15	-0.17 (-4.5 to 2.2)	0.48	-1.20–0.86	0.7235
cSaO ₂ (%)	97.2 (96.6–98.0)	15	37.8 (17.3–64.2)	15	70.4 (43.1–84.8)	15	32.6 (-7.4 to 62.8)	4.1	23.6–41.5	0.0008 ^b

^a Resp. rate indicates respiratory rate; Rectal temp., rectal temperature; SpO₂, oxygen saturation; BP systol, systolic blood pressure; BP diastol, diastolic blood pressure; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; Na⁺, sodium ions; K⁺, potassium ions; Ca²⁺, calcium ions; cHct, calculated hematocrit; cHgb, calculate hemoglobin; cHCO₃⁻, calculated bicarbonate ions; cTCO₂, concentration of total carbon dioxide; cBe ECF, calculated base excess in extracellular fluid; cSaO₂, arterial hemoglobin oxygen saturation.

^b Mean differences assessed using the Wilcoxon matched-pairs signed-ranked test because the assumption of normality was violated.

^c Dashes indicate no values recorded.

animals. Median time for all animals to walking or running was 110 sec (range 71–247 sec) after i.v. administration of the reversal agent. No reanarctization was seen.

DISCUSSION

Results indicate that etorphine and midazolam anesthesia in white rhinoceroses is a safe, effective regime that provides good muscle relaxation. However, the median time from darting to recumbency in the animals not roped down was 548 sec (range 361–787 sec); this value was longer than in a similar study in game ranched animals by using etorphine and azaperone and also darted from a vehicle (405 sec, range 140–967).³ The reason for this is unknown. Although midazolam is known to have a rapid onset of action,²⁰ a slower absorption of midazolam might be a possible explanation.

Combining midazolam with etorphine seemed to improve muscle relaxation in all 19 studied animals regardless of the recumbency position. Eighteen animals were relaxed, without any visible tremors, paddling, or head shaking. This is a substantial improvement compared with other studies using etorphine and azaperone, where ear twitching, limb rigidity, and muscle tremors were observed in the study animals.^{3,9}

The analyses of arterial blood gases revealed severe hypoxemia ($\text{PaO}_2 < 70$ mm Hg), hypercapnia, and respiratory acidosis in all white rhinoceroses anesthetized with etorphine and midazolam in this study. All cardiopulmonary parameters, including pH, PaO_2 , PaCO_2 , SaO_2 , respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure remained outside normal reference ranges¹⁰ during the entire procedure, before and 10 min after the administration of butorphanol. The mean PaCO_2 value in healthy conscious white rhinoceroses was 49 mm Hg.¹⁰ The very high PaCO_2 values found in the animals (even above 60 mm Hg) and low PaO_2 values were likely caused by hypoventilation and ventilation-perfusion imbalance.^{3,18,30} Pulmonary hypertension caused by etorphine might also play a significant role in decreasing the movement of oxygen, thereby causing hypoxemia, and similar to the findings in goats.¹⁷ No clinical difference was found in the PaO_2 and cSaO_2 with etorphine and midazolam compared with etorphine and azaperone (PaO_2 , 26.9 and 26.7 mm Hg; cSaO_2 , 37.8 and 38.3%, respectively, before butorphanol; and PaO_2 , 44.2 and 45.5 mm Hg; cSaO_2 , 70.4 and 73.36%, respectively, after butorphanol).³ Despite the persistent hypoxemia, hypercapnia, and metabolic acidosis, the cardiopulmonary and bio-

chemical parameters in this study significantly improved 10 min after administration of butorphanol i.v. Improvements in respiration rate, heart rate, pH, PaCO_2 , PaO_2 , and cSaO_2 , after administration of butorphanol, were greater in rhinoceroses anesthetized with etorphine and midazolam than with etorphine and azaperone.³ These findings suggest that the excellent relaxation properties of midazolam, which is more slowly absorbed than etorphine, might have a positive effect on these parameters.

Improved oxygenation was found in animals in sternal than lateral recumbency, which is similar to the findings in other studies in white rhinoceroses and black rhinoceroses (*Diceros bicornis*).^{3,28} A smaller dead space in sternal position is a likely explanation for this improvement.^{3,28} The positive effect of sternal recumbency might also be explained by improved oxygenation due to increased ventilation and blood flow in both sides of the lungs, as was previously reported in black rhinoceroses.^{3,19}

Recumbent animals in this study were found to be more hypoxemic after butorphanol (mean $\text{PaO}_2 = 44.2$) than recumbent free-ranging animals before butorphanol in the studies by Miller et al. and Wenger et al. (mean $\text{PaO}_2 = 58.9$ and 50.95, respectively).^{18,30} In the Wenger study, 4.5–5 mg of detomidine was also included in the dart, which is likely to influence these results.³⁰ White rhinoceroses anesthetized with etorphine and azaperone on the same premises were also more hypoxic (mean $\text{PaO}_2 = 45.0$) after butorphanol than those in a previously mentioned study.³ The game-ranch animals in the present study were heavier and more prone to ventilation-perfusion mismatch than free-ranging rhinoceroses and might offer an explanation for this finding. The present study used an epoc host blood gas analyzer, whereas the other studies used an iSTAT blood gas analyzer. However, evaluation of the analyzer revealed clinically acceptable agreement compared with a hospital blood gas analyzer, the Radiometer ABL 77, with equine blood samples.² Blood gas values were not corrected for patient temperature and are representative of the analyzers default temperature of 37°C. Correction was not considered following other similar research³ because the time between gas analyses was only 10 min. In addition, corrections are not considered to be clinically more useful¹¹ and uncorrected values should be routinely reported.²⁹

The lactate and base excess levels in this study were low compared with free-roaming rhinoceroses darted from a helicopter,^{18,30} and they were similar to those of boma-trained animals.⁹ The

relatively quiet approach by vehicles and minimal predarting excitement in the game-ranched animals in comparison to animals chased by a helicopter is a likely explanation for this difference. The excellent muscle relaxation and calming properties of midazolam might be a reason why lactate levels were even lower in this study than those in rhinoceroses anesthetized with etorphine and azaperone.³

One limitation of this study was the absence of controls (animals receiving i.v. saline instead of butorphanol). The lack of controls was justified because butorphanol has been reported to improve blood oxygenation in recumbent rhinoceroses.^{3,5} Therefore, we wanted to minimize anesthetic risk, and we made the assumption that physiologic and blood gas parameters would not change significantly for animals not receiving butorphanol.

In conclusion, the data suggest that midazolam and etorphine together offer an effective alternative anesthetic regime for white rhinoceroses. This combination seems to provide improved muscle relaxation in both sternal and lateral recumbency, but it has a slower induction period compared to azaperone and etorphine anesthesia. Butorphanol administered i.v. at the ratio of 10 mg of butorphanol to 1 mg of etorphine in the study animals seemed to induce a direct μ antagonist effect similar to the findings in the study using etorphine and azaperone.³ This was reflected in a decrease in heart rate and an increase in respiratory rate and significant improvements in pH, PaO₂, PaCO₂, and SaO₂. However, these improvements in cardiopulmonary parameters were greater in this study than when butorphanol was administered to white rhinoceroses anesthetized with etorphine and azaperone.³ Although improvements did occur, the severe hypoxemia and hypercapnia in all animals during the entire procedure in this study highlights the importance of continuing to investigate ways to improve cardiopulmonary parameters in anesthetized white rhinoceroses.

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LITERATURE CITED

1. Bapodra P, Cracknell J, Wolfe BA. Comparison of butorphanol-detomidine versus butorphanol-azaperone for the standing sedation of captive greater one-horned rhinoceroses (*Rhinoceros unicornis*). *J Zoo Wildl Med.* 2014;45:60–68.
2. Bardell D, West E, Senior JM. Evaluation of a new handheld point-of-care blood gas analyser using 100 equine blood samples. In: *Proc Assoc Vet Anaesth Congr*; 2011. p. 28.
3. Boardman WSJ, Caraguel CGB, Raath JP, van Zijll Langhout MH. Intravenous butorphanol improves cardiopulmonary parameters in game ranched white rhinoceroses (*Ceratotherium simum*) immobilized with etorphine and azaperone. *J Wildl Dis.* 2014;50: 849–857.
4. Branson KR, Cross ME. Opioid agonist and antagonist. In: Richards HR (ed.). *Veterinary pharmacology and therapeutics.* 8th ed. Ames (IA): Iowa State University Press; 2001. p. 268–298.
5. Burroughs R, Hofmeyr M, Morkel P, Kock MD, Kock R, Meltzer D. White or square lipped rhinoceros (*Ceratotherium simum*). In: Kock MD, Burroughs R (eds.). *Chemical and physical restraint of wild animals.* 2nd ed. Greyton (South Africa): International Wildlife Veterinary Services; 2012. p. 223–234.
6. Bush M, Citino SB, Grobler D. Improving cardiopulmonary function for a safer anesthesia of white rhinoceroses (*Ceratotherium simum*): use of opiate cocktails to influence receptor effects. *Proc Am Assoc Zoo Vet*; 2005. p. 259–260.
7. Bush M, Citino SB, Lance WR. The use of butorphanol in anesthesia protocols for zoo and wild animals. In: Miller RE, Fowler ME (eds.). *Zoo and wild animal medicine, Volume 7, Current therapy.* New York (NY): Elsevier; 2011. p. 596–603.
8. Bush M, Raath JP, Grobler D, Klein L. Severe hypoxaemia in field-anesthetized white rhinoceroses (*Ceratotherium simum*) and effects of using tracheal insufflation of oxygen. *J S Afr Vet Assoc.* 2004;75(2): 79–84.
9. Buss P, Olea-Popelka F, Meyer L, Hofmeyr J, Mathebula N, Kruger M, Brüns A, Martin L, Miller M. Evaluation of cardiorespiratory, blood gas, and lactate values during extended immobilization of white rhinoceroses (*Ceratotherium simum*). *J Zoo Wildl Med.* 2015;46:224–233.
10. Citino SB, Bush MR. Reference cardiopulmonary physiologic parameters for standing, unrestrained white rhinoceroses (*Ceratotherium simum*). *J Zoo Wildl Med.* 2007;38:375–379.
11. Eskaros SM, Papadakos PJ, Lachmann B. Respiratory monitoring. In: Miller RD (ed.). *Miller's anesthesia.* 7th ed., Chapter 44. Philadelphia (PA): Churchill Livingstone/Elsevier; 2010. p. 1415.
12. Hattingh J, Knox CM, Raath JP. Arterial blood pressure and blood gas composition of white rhinoceroses under etorphine anaesthesia. *S Afr J Wildl Res.* 1994;24:12–14.

13. Haw A, Hofmeyr M, Fuller A, Buss P, Miller M, Fleming G, Meyer L. Butorphanol with oxygen insufflation corrects etorphine-induced hypoxaemia in chemically immobilized white rhinoceros (*Ceratotherium simum*). *BMC Vet Res*. 2014;10:253–261.
14. Heard DJ, Olsen JH, Stover J. Cardiopulmonary changes associated with chemical anesthesia and recumbency in a white rhinoceros (*Ceratotherium simum*). *J Zoo Wildl Med*. 1992;23:197–200.
15. Kock MD, Morkel P, Atkinson M, Foggin C. Chemical immobilization of free ranging white rhinoceros (*Ceratotherium simum*) in Hwange and Matobo national parks, Zimbabwe, using combination of etorphine (M99), fentanyl, xylazine, and detomidine. *J Zoo Wildl Med*. 1995;26:207–219.
16. Melzter D, Burroughs R, Morkel P. Applied pharmacology. In: Kock MD, Meltzer D, Burroughs R (eds.). *Chemical and physical restraint of wild animals. A training and field manual for African species*, Chapter 4. Greyton (South Africa): IWVS; 2006. p. 64.
17. Meyer LCR, Hetem RS, Mitchell D, Fuller A. Hypoxia following etorphine administration in goats (*Capra hircus*) results more from pulmonary hypertension than from hypoventilation. *BMC Vet Res*. 2015;11:18.
18. Miller M, Buss P, Joubert J, Mathebula N, Kruger M, Martin L, Hofmeyr M, Olea-Popelka F. Use of butorphanol during immobilization of free-ranging white rhinoceroses (*Ceratotherium simum*). *J Zoo Wildl Med*. 2013;44:55–61.
19. Morkel PvdB, Radcliffe RW, Jago M, du Preez P, Flaminio MJBF, Nydam DV, Taft A, Lain D, Miller MM, Gleed RD. Acid-base balance and ventilation during sternal and lateral recumbency in field immobilized black rhinoceroses (*Diceros bicornis*) receiving oxygen insufflation: a preliminary report. *J Wildl Dis*. 2010;46:236–245.
20. Muir WW, Hubbell JAE, Bednarski RM. 2007. *Handbook of veterinary anesthesia*. (Columbus, OH): Mosby Elsevier; 2007. p. 35–36.
21. Paterson J. Capture myopathy. In: West G, Heard D, Caulkett N (eds.). *Zoo animal and wildlife immobilization and anesthesia*. 2nd ed., Chapter 12. Ames (IA): Wiley-Blackwell; 2014. p. 176.
22. Plumb DC. 1995. Midazolam. In: Plumb DC (ed.). *Veterinary drug handbook*. 2nd ed. Ames (IA) Iowa University State Press; 1995. p. 457–459.
23. Portas TJ. A review of drugs and techniques used for sedation and anaesthesia in captive rhinoceros species. *Aust Vet J*. 2004;82:542–549.
24. Portas TJ, Hermes R, Bryant BR, Goritz F, Ladds P, Hildebrandt TB. Seminoma in a southern white rhinoceros (*Ceratotherium simum simum*). *Vet Rec*. 2005; 157:556–558.
25. Raath JP. Anesthesia of white rhinoceros. In: Fowler ME, Miller RE (eds.). *Zoo and wild animal medicine*, Volume 4, Current therapy. Philadelphia (PA): W. B. Saunders Co.; 1999. p. 556–561.
26. Radcliffe RW, Ferrell ST, Childs SE. Butorphanol and azaperone as a safe alternative for repeated chemical restraint in captive white rhinoceros (*Ceratotherium simum*). *J Zoo Wildl Med*. 2000;31:196–200.
27. Radcliffe RW, Morkel PM. Rhinoceroses. In: West G, Heard D, Caulkett N (eds.). *Zoo animal and wildlife anesthesia and anesthesia*. 2nd ed, Chapter 54. Ames (IA): Wiley-Blackwell; 2014. p. 741–771.
28. Radcliffe RW, Morkel P, Jago M, Taft AA, du Preez P, Miller MA, Candra D, Nydam DV, Barry JS, Gleed RD. Pulmonary dead space in free-ranging immobilized black rhinoceroses (*Diceros bicornis*) in Namibia. *J Zoo Wildl Med*. 2014;45:263–271.
29. Shapiro BA, Peruzzi WT, Templin R. Temperature correction of blood gas values. In: Shapiro BA, Peruzzi WT, Templin R. (eds.). *Clinical application of blood gasses*. 5th ed., Chapter 19. St. Louis (MO): Elsevier; 1994. p. 227–233
30. Wenger S, Boardman W, Buss P, Govender D, Foggin C. The cardiopulmonary effects of etorphine, azaperone, detomidine, and butorphanol in field-anesthetized white rhinoceroses (*Ceratotherium simum*). *J Zoo Wildl Med*. 2007;38:380–387.

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