Journal of Zoo and Wildlife Medicine 44(1): 55–61, 2013

USE OF BUTORPHANOL DURING IMMOBILIZATION OF FREE-RANGING WHITE RHINOCEROS (*CERATOTHERIUM SIMUM*)

Michele Miller, D.V.M., Ph.D., Peter Buss, B.V.Sc., M.Med.Vet., Jenny Joubert, B.Tech. (Vet), B.Sc.Hon., Nomkhosi Mathebula, B. Tech. (Vet), Marius Kruger, B.Sc.Hon., M.Sc., Laura Martin, B.S., Markus Hofmeyr, B.V.Sc., and Francisco Olea-Popelka, D.V.M., Ph.D.

Abstract: Forty free-ranging white rhinoceros (*Ceratotherium simum*) were anesthetized with etorphine, azaperone, and hyaluronidase in Kruger National Park, South Africa, between February and August 2009. Eighteen rhinoceros received butorphanol in the dart combination, and 22 rhinoceros had butorphanol administered intravenously within 15 min of darting. Body position, blood gas values, heart rate, respiratory rate, and temperature were measured at two time points after darting, approximately 10 min apart (sample 1 mean collection time after darting, 9.4 ± 2.7 min; sample 2 mean collection time, 18.6 ± 2.8 min). A significant number of field-captured rhinoceros remained standing at the first sample period when butorphanol was administered in the dart. Higher median values for arterial partial pressure of oxygen (PaO_2) in combination with lower arterial partial pressure of carbon dioxide ($PaCO_2$) in standing versus recumbent rhinoceros suggested improved ventilation in this posture ($P < 0.05$). When the effect of time, body position, and age was controlled, median values for respiratory rate, lactate, and pH were better in rhinoceros that received butorphanol in the dart ($P < 0.05$). There was also a trend toward higher median values for SO_2 and bicarbonate in rhinoceros receiving butorphanol in the dart. Intravenous administration of butorphanol resulted in significantly decreased median $PaCO_2$ and heart rate in recumbent rhinoceros ($P < 0.05$) without changes in PaO_2 between sample periods 1 and 2. However, rhinoceros remained hypoxemic during the short anesthetic procedure despite butorphanol administration. Preliminary results suggest that administration of butorphanol (either in the dart or intravenously) improves some metabolic parameters in free-ranging recumbent white rhinoceros without significantly affecting ventilation. It is hypothesized that this may be due to a lighter state of immobilization. Addition of butorphanol to the dart provides handling and physiologic advantages because the majority of rhinoceros remain standing.

Key words: blood gas, butorphanol, cardiorespiratory effect, *Ceratotherium simum*, immobilization, white rhinoceros.

INTRODUCTION

Chemical immobilization of white rhinoceros (*Ceratotherium simum*) is routinely performed for medical procedures, translocation, and snare removal. However, the drugs used often result in significant respiratory depression, leading to hypoxemia, hypercapnia, and potential complications associated with decreased tissue oxygenation.[1,4,10] Partial opioid agonist-antagonists such as nalorphine are often administered to counteract these effects. Because of the lack of availability of some of these agents and unsatisfactory responses, other methods for improving ventilation in anesthetized rhinoceros are being studied.[11] Butorphanol has been used anecdotally as a partial agonist-antagonist and to aid in minimizing complications such as hypoventilation.[14] However, route and timing of administration and a critical assessment of clinical effect have not been completed under field conditions. In this paper, the clinical outcomes of butorphanol were compared when administered in the immobilizing drug combination in the dart or intravenously after immobilization of free-ranging white rhinoceros.

From Veterinary Wildlife Services, South African National Parks, Kruger National Park, Private Bag X402, Skukuza, 1350, South Africa (Buss, Joubert, Mathebula, Kruger, Hofmeyr); Palm Beach Zoo, 1301 Summit Boulevard, West Palm Beach, Florida 33405, USA (Miller); and Department of Clinical Sciences, Animal Population Health Institute, College of Veterinary Medicine and Biomedical Science, Colorado State University, Fort Collins, Colorado 80523, USA (Martin, Olea-Popelka). Correspondence should be addressed to Dr. Miller (mmiller@palmbeachzoo.org).

MATERIALS AND METHODS

Study area and sample population

The study animals were 40 free-ranging white rhinoceros immobilized during game capture operations in Kruger National Park (23°49′60′′S, 31°30′0′′E), South Africa, between February and August 2009. Ambient temperatures were typically 20–30°C. All animals were grouped in age categories based on size: juveniles (calf with dam),

young or subadult (2.5–7 yr of age), or adult (older than 7 yr). Animals appeared healthy based on body condition and physical examination. There were 2 juveniles, 19 subadults, and 19 adults, with 14 males and 26 females included in the study. Twenty-two rhinoceros received a combination of etorphine (Novartis, Kempton Park, 1619 South Africa; 9.8 mg/ml), azaperone (Stresnil, Janssen Pharmaceutical Ltd., Halfway House, 1685 South Africa, 40 mg/ml), and hyaluronidase (lyophilized hyalase, Kyron Laboratories, Benrose, 2011 South Africa) in the dart with butorphanol (Kyron Laboratories; 50 mg/ml) administered i.v. within 15 min of darting (treatment group 1). Etorphine, azaperone, butorphanol, and hyaluronidase were administered in a single dart to 18 rhinoceros (treatment group 2). Doses were based on standardized age categories: juvenile doses: 1.5 mg of etorphine, 40 mg of azaperone, and 5,000 international units (IU) of hyaluronidase; subadult doses: 2.5–3.5 mg of etorphine, 20–40 mg of azaperone, and 5,000 IU of hyaluronidase; and adult doses: 3.5–4.2 mg of etorphine, 40 mg of azaperone, and 5,000 IU of hyaluronidase. Butorphanol was either added directly to the dart or administered i.v. in an auricular vein after the first arterial blood sample was collected (sample period 1). The butorphanol dose administered was calculated at 20 mg/mg etorphine.

Animals were located and darted using a helicopter according to the South African National Parks standard protocol. Drugs were delivered remotely using 3.0-ml plastic darts with a 60-mm uncollared needle delivered by compressed air rifle (DAN-INJECT, International S.A., Skukuza, 1350 South Africa).

Signs of induction were observed from the helicopter and consisted of slowing or ataxia. Time to stopping refers to time from darting until recumbency or the animal stopping without any further forward movement while remaining on its feet. The distance travelled after darting was estimated using the global positioning device in the helicopter and refers to the distance until the animal stopped.

After sample collection, the rhinoceros was loaded into a transport crate. All animals received diprenorphine i.v. (M5050, Novartis Animal Health, Kempton Park, 1619 South Africa; 12 mg/ml) (6 mg for juveniles, 12 mg for subadults and adults) and 50 mg zuclopenthixol acetate i.m. (Clopixol-Acuphase, H. Lundbeck Pty. Ltd., North Riding, 0040 South Africa; 50 mg/ml) after being placed in the crates.

Sample collection and assays

Arterial blood samples were collected in 1-ml heparinized syringes from the medial auricular artery during two time periods and are presented as mean (SD): sample period 1, 9.4 min (2.7) and sample period 2, 18.6 min (2.8). In the case of rhinoceros in treatment group 1 (i.v. butorphanol), the first arterial sample was collected before administration of butorphanol. All arterial blood samples were immediately analyzed using a portable blood gas analyzer (iSTAT®1 Handheld Clinical Analyzer, Heska Corporation, Loveland, Colorado 80538, USA) using the CG4+ cartridge (iSTAT CG4+ cartridges, Heska Corporation). Arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), pH, and lactate were measured by the portable blood gas analyzer. Base excess (BE), bicarbonate (HCO_3), and arterial hemoglobin oxygen saturation (SaO_2) were automatically calculated values. Samples were corrected to body temperature, but only noncorrected samples are presented because not all rhinoceros had temperatures taken at all sample periods. A pulse oximeter (TidalGuard™, SHARN Veterinary Inc., Herrsching, 82211 Germany) was placed on the conjunctiva and used to determine heart rate and oxygen saturation. Heart rate also was measured by auscultation with a stethoscope. Respiratory rate was measured by visual assessment of thoracic and abdominal excursions and air movement at the nares.

Data analysis

STATA (Stata Statistical Software Release 11, Stata Corporation, College Station, Texas 77840, USA) was used for the statistical analysis. The distribution of each cardiorespiratory parameter in this study was evaluated for normality, at first visualizing the box plots and normal quantile plot, and more formally using the Shapiro–Wilk normality test. Means, standard deviations, and medians were calculated for descriptive purposes for rhinoceros in different treatment groups at each sample period (Table 1). Due to the relatively small sample size obtained for this study, nonparametric statistical tests were used to analyze the data. The Wilcoxon rank sum test was used to compare the induction time between rhinoceros in each treatment group as well as the distance travelled before induction. Fisher's exact test was used to compare the proportion of rhinoceros standing at the first sample period in each treatment group. To compare cardiorespiratory parameters, as a first screening step, a

Table 1. Descriptive statistics (mean, SD, median, and *n*) for white rhinos under two different immobilization protocols at two different time points by body position.

	Heart rate	Respiratory rate	Body temperature	$PaCO_2$	PaO_2	BE_{ecf}	HCO_3	TCO_2	SaO_2	Lactate	pH	Corrected pH
Treatment 1												
Time 1												
Standing												
Mean	97.33	12.00	36.60	61.10	50.33	–6.33	22.17	24.00	70.00	12.89	7.17	7.21
SD	36.95	0.00	0.92	20.14	16.01	8.33	7.84	8.72	19.29	3.25	0.06	—
Median	76.00	12.00	36.40	52.60	51.00	–9.00	19.00	20.00	78.00	13.38	7.18	7.21
n	3	3	3	3	3	3	3	3	3	3	3	1
Recumbent												
Mean	108.56	12.00	36.99	61.87	50.95	–6.79	22.08	23.84	71.37	12.91	7.15	7.15
SD	27.23	3.16	0.74	7.90	10.31	7.37	5.83	6.05	9.66	5.59	0.11	0.11
Median	116.00	12.00	37.00	63.80	51.00	–7.00	22.40	24.00	71.00	14.15	7.17	7.16
n	18	17	19	19	19	19	19	19	19	18	19	11
Time 2												
Standing												
Mean	60.00	10.00	36.40	57.90	67.00	–10.00	19.50	21.00	86.00	12.38	7.14	—
SD	—	—	—	—	—	—	—	—	—	—	—	—
Median	60.00	10.00	36.40	57.90	67.00	–10.00	19.50	21.00	86.00	12.38	7.14	—
n	1	1	1	1	1	1	1	1	1	1	1	0
Recumbent												
Mean	79.33	10.33	37.06	54.50	52.67	–6.67	21.41	23.11	76.11	11.63	7.19	7.19
SD	13.81	2.38	0.60	7.53	9.52	6.75	5.42	5.59	8.84	5.26	0.10	0.10
Median	72.00	10.00	37.00	55.55	48.50	–650	21.15	23.00	76.00	11.37	7.22	7.21
n	18	18	17	18	18	18	18	18	18	17	18	10
Treatment 2												
Time 1												
Standing												
Mean	95.33	12.91	37.01	50.76	60.54	–4.00	23.11	24.71	84.31	8.27	7.26	7.26
SD	18.71	4.13	0.65	8.80	12.01	6.94	6.05	6.22	8.14	6.14	0.07	0.07
Median	103.00	12.00	36.90	53.60	60.00	–3.00	24.35	26.00	86.00	7.49	7.27	7.26
n	12	11	14	14	13	14	14	14	13	8	14	12
Recumbent												
Mean	112.00	14.50	37.33	59.23	48.50	0.00	27.08	28.50	68.25	4.09	7.27	7.23
SD	42.46	3.42	0.38	10.28	19.43	3.16	1.93	1.73	29.23	3.75	0.10	0.06
Median	126.00	15.00	37.50	60.40	51.00	0.50	27.70	29.00	76.50	2.43	7.25	7.19
n	4	4	3	4	4	4	4	4	4	3	4	3
Time 2												
Standing												
Mean	64.67	14.00	36.83	54.97	59.50	1.17	27.75	29.17	86.50	1.57	7.31	7.30
SD	11.02	2.00	0.63	9.79	6.53	2.93	2.73	3.19	3.73	1.80	0.04	0.03
Median	64.00	14.00	36.75	54.25	57.50	1.50	27.90	29.50	85.50	1.57	7.32	7.30
n	3	5	6	6	6	6	6	6	6	2	6	5
Recumbent												
Mean	94.50	12.00	36.70	56.23	52.00	–3.67	23.97	25.33	77.67	9.46	7.23	7.23
SD	33.36	5.35	0.97	4.62	6.93	5.86	4.92	4.93	8.62	4.01	0.08	0.07
Median	96.00	12.50	37.00	58.70	48.00	–6.00	21.80	23.00	76.00	10.31	7.24	7.24
n	4	4	4	3	3	3	3	3	3	3	3	3

univariable analysis was conducted. The nonparametric Wilcoxon rank sum test was used to compare the median values for each cardiorespiratory parameter between rhinoceros in the same body position, between different treatment groups at each sample period, separately. Second, to account for repeated measurements (lack of independence among samples taken from the same animal at different sample periods) and to control for different factors potentially affecting the values of cardiorespiratory parameters measured, a multiple linear regression generalized estimating equation was used to evaluate the effect of treatment on the cardiorespiratory

parameters while controlling (adjusting) for the effect of time (sample period), body position, and age category. The multivariable analysis was conducted using ranks (nonparametric equivalent) to compare the median values of each cardiorespiratory parameter. Statistical significance was set at $P \leq 0.05$ for all statistical tests.

RESULTS

Effect of route of butorphanol administration on induction

The overall mean induction time for all rhinoceros in the study was 5.4 min (95% confidence interval [CI] = 4.9–6.0). There was a significant difference in the median induction time between treatment groups ($P = 0.0035$). Rhinoceros receiving butorphanol in the dart (treatment group 2) had a longer median induction time of 6 min compared with 4.6 min for rhinoceros that received butorphanol postimmobilization (treatment group 1). However, there was no significant difference in the distance travelled after darting rhinoceros under different treatments (treatment i.v. group 1 median, 500 m; treatment group 2 median, 600 m; $P = 0.58$).

The majority (14/18, 77.8%) of treatment group 2 rhinoceros (butorphanol in the dart) remained standing at the first sample period, compared with only 3/22 (14%) of the rhinoceros in the postimmobilization butorphanol group (treatment group 1) ($P < 0.0001$). By the second sample period, 6/10 (60%) of treatment group 2 rhinoceros for which samples were available remained standing compared with 1/19 (5.2%) animals that had i.v. butorphanol (treatment group 1).

Effect of route of butorphanol administration on cardiorespiratory parameters in standing rhinoceros

During the first sample period, median heart rate, respiratory rate, body temperature, $PaCO_2$, PaO_2, SaO_2, base excess, HCO_3, and lactate did not show any statistically significant differences ($P > 0.05$) between rhinoceros receiving butorphanol in the dart (treatment group 2) and those that had not yet received butorphanol (treatment group 1) (Table 1). The median pH was significantly higher in the rhinoceros that received butorphanol in the dart compared with those that did not (7.27 vs. 7.18, respectively; $P = 0.044$).

Within treatment groups, treatment group 2 (butorphanol administered in dart) animals had a decreased median heart rate (103 vs. 64 beats/min; $P = 0.002$) between sample periods 1 and 2. The sample size for standing rhinoceros in treatment group 1 (i.v. butorphanol) was too small to assess the effect between sample times (only one standing rhino in treatment group 1 at the second sample period).

Effect of route of butorphanol administration on cardiorespiratory parameters in recumbent rhinoceros

During sample period 1, similar to standing rhinoceros, there were no significant differences ($P > 0.05$) in median values for heart rate, respiratory rate, body temperature, $PaCO_2$, PaO_2, and SaO_2 between rhinoceros receiving butorphanol in the dart (treatment group 2) and those that had not yet received butorphanol (treatment group 1) (Table 1). However, significantly lower lactate (2.43 vs. 14.14 mmol/L; $P = 0.027$) and higher pH (7.25 vs. 7.17; $P = 0.026$) were observed between rhinoceros receiving butorphanol in the dart (treatment group 2) and those that had not yet received butorphanol (treatment group 1) (Table 1). A comparison of treatment groups at the second sample period showed no significant differences in any of the measured values.

When values were compared in recumbent rhinoceros that received i.v. butorphanol (treatment group 1) between sample periods 1 and 2, the only significant changes were decreases in median heart rate (116 vs. 72 beats/min; $P = 0.002$) and median $PaCO_2$ (63.8 vs. 55.6 mm Hg; $P = 0.004$). No significant differences were found in any measured values in recumbent treatment group 2 rhinoceros between sample periods 1 and 2.

Effect of route of butorphanol administration on cardiorespiratory parameters adjusting for the effect of each rhinoceros, time, body position, and age category

The multivariable analysis results (adjusting for repeated measurements within rhinoceros) indicates that after controlling for the effect of time, body position, and age category, rhinoceros receiving butorphanol in the dart had significantly lower median value for lactate ($P < 0.001$) and higher median respiratory rate ($P = 0.036$) and pH ($P < 0.001$) compared with treatment group 1 rhinoceros (butorphanol i.v.). When controlling for the effect of treatment, body position, and age category, samples taken from rhinoceros at sample period 2 had significantly lower median values for heart rate ($P < 0.001$), $PaCO_2$ ($P = 0.018$), and lactate ($P < 0.001$) and higher pH ($P < 0.001$) compared with samples taken from rhinoceros at

sample period 1. There was a trend toward a higher median SaO_2 ($P = 0.063$) in sample period 2 compared with period 1.

When controlling for the effect of treatment, sample period, and age category, recumbent rhinoceros had significantly lower median values for PaO_2 ($P = 0.05$) and SaO_2 ($P = 0.014$) and higher $PaCO_2$ ($P = 0.05$) compared with standing rhinoceros ($P \leq 0.05$).

DISCUSSION

Anesthesia in white rhinoceros is frequently complicated by depressed respiratory function and its sequelae. Free-ranging rhinoceros often receive higher doses of potent opioids to minimize the potential for hyperthermia, lactic acidosis, and capture myopathy that can result from prolonged induction times. However, these doses are also more likely to cause hypoventilation, hypoxemia, and decreased tissue oxygenation.[1] Therefore, most animals receive partial agonist-antagonists, supplemental oxygen, or other treatments to alleviate these problems while immobilized.[1,11]

Etorphine exerts its actions as a μ-, κ, and δ-receptor agonist.[5] The μ-receptors are primarily responsible for respiratory depression and some analgesia, and κ-receptors are primarily responsible for sedation and analgesia. Nalorphine, a partial opioid agonist-antagonist, has been used in white rhinoceros for reversal of respiratory depression, but it is no longer commercially available.[6] More potent antagonists, such as diprenorphine and naloxone, have been titrated to effect for similar purposes, but they are potentially more dangerous to use in the field. Therefore, the rationale for using butorphanol, also a partial agonist-antagonist, was to alleviate some of the respiratory depressive effects of etorphine through antagonism at the μ2-receptor while synergizing the sedative and analgesic effects at the κ-receptor. The current study investigated a practical approach of examining the effect of butorphanol on clinical effects through a retrospective review of white rhinoceros field immobilizations in which butorphanol was included in the immobilizing drug combination or administered i.v. after immobilization.

Butorphanol is reported to be a mixed opioid agonist-antagonist, specifically a weak μ-receptor antagonist and κ-agonist.[7] However, in cases in which butorphanol is used alone or in combination with other classes of drugs for sedation or immobilization, respiratory depression may be observed. Addition of butorphanol in detomidine-sedated horses (*Equus caballus*) resulted in decreased ventilation, increased $PaCO_2$, and increases V_A/Q mismatch.[12] Intravenous butorphanol did not result in any significant cardiorespiratory effects as measured by systemic and pulmonary blood pressures and by blood gases in isoflurane-anesthetized alpacas (*Vicugna pacos*).[13] These studies contradict the hypothesis that butorphanol improves ventilation as a μ-antagonist.

Other reports have shown that butorphanol also may have activity as a low efficacy μ-agonist (respiratory depression, μ2). Studies in humans (*Homo sapiens*) and rhesus macaques (*Macaca mulatta*) using specific μ-receptor agonist blockers suggest that butorphanol has μ-agonist properties.[15] Therefore, the pharmacology of butorphanol is more complex than previously thought and may depend on species, dose, and interaction with other opioids.

Field use of butorphanol to improve ventilation has anecdotally been observed, although one report saw no benefits in white rhinoceros, a finding that was attributed to the inclusion of detomidine.[16] However, in the case of the study reported above, butorphanol may have been acting as a weak μ-agonist more similarly to that observed in humans and macaques.[15]

In this study, several statistically significant differences were observed in the measured parameters. Few significant differences were observed with the univariable analysis. For example, in recumbent rhinoceros, during the first sample period, lower lactate values and higher pH values were obtained from rhinoceros with butorphanol added in the dart. Also, in recumbent rhinoceros in treatment group 1, a decrease in median heart rate and $PaCO_2$ values was observed at sample period 2. Comparing measured parameters between rhinoceros in different treatment groups and separately at different sample periods for rhinoceros in the same body position eliminated potential confounding effects of this body position, due to the different distribution of standing and recumbent rhinoceros in each treatment group.

To account (adjust) for all factors in the analysis (treatment, body position, sample period, age category, and repeat sampling of individuals), a multivariable model was constructed. The adjusted multivariable analysis permitted unbiased comparisons between treatment groups (and between sample periods, and between body positions) while controlling for the combined effect of all the parameters included in the model. There was no difference in the distribution of sex among rhinoceros in different treatments groups; hence, sex was not included in our models.

The adjusted results indicated that rhinoceros receiving butorphanol in the dart overall had significantly lower median values for lactate and higher median respiratory rate and pH compared with animals receiving buthorphanol i.v. Although not statistically significant, rhinoceros receiving butorphanol in the dart also had higher median base excess ($P = 0.076$), SaO_2 ($P = 0.13$), and HCO_3 ($P = 0.13$).

It is worth noting that lack of statistically significant differences may be due to the relatively small sample size available for some of the comparisons performed in this study, a limitation of this retrospective field study. However, we think it is important to emphasize that even though not statistically significant, our results indicate that some of the trends recorded (e.g., SaO_2 and HCO_3) may be physiologically important between treatment groups.

Standing rhinoceros created logistical challenges in obtaining samples, especially at the second sample period when they were already being loaded into crates, as was reflected in different number of measurements at different times. One of the difficulties in making comparisons in this study was the high proportion of white rhinoceros that remained standing when butorphanol was administered in the dart compared with those that received butorphanol postimmobilization and became recumbent (this was controlled or adjusted both for the univariable and multivariable analysis). However, from the point of view of managing rhinoceros, having a large animal standing is more physiologically normal. The advantages of this posture over recumbency were shown by the significantly higher median PaO_2 and SaO_2 and lower $PaCO_2$ in the standing rhinoceroses in this study.

Rhinoceros receiving butorphanol in the dart took longer to stop; however, they did not travel any additional distance, suggesting that animals were less likely to experience lactic acidosis and hyperthermia due to decreased intensity of exertion during induction. They also had a greater propensity to remain standing, thereby facilitating ventilation.[2,9] The lower lactate and higher pH in this treatment group was statistically significant and supported this hypothesis. Even if the rhinoceros that received butorphanol in the dart became recumbent, these same metabolic values were better than those of recumbent animals that did not receive butorphanol. This finding suggests that butorphanol had a beneficial effect on metabolic parameters, possibly through decreased intensity of exertion during induction.

Standing animals could be managed for sampling and leading to the transport crate; however, caution is advised in choosing this regimen without experienced staff. In addition, rhinoceros that became recumbent could be stimulated to stand if they had received butorphanol, indicating that administration of this drug induces a lighter plane of immobilization. Therefore, one alternative hypothesis is butorphanol causes a slightly lighter level of sedation, allowing the animal to metabolically compensate while remaining immobilized.

Intravenous administration of butorphanol may have had some physiologic effect on recumbent white rhinoceros because median heart rate and $PaCO_2$ decreased between the first and second samples (mean difference of 9.2 min between samples). These changes remained significantly different between sample periods after controlling for the effect of treatment, body position, and age. Although SaO_2 tended to increase over time, it was not statistically significant ($P = 0.063$). Although the decrease in $PaCO_2$ is consistent with improved ventilation, there was not a concurrent increase in PaO_2. This finding may be due to ventilation–perfusion mismatch in recumbent rhinoceros, increased oxygen demand by tissues recovering from capture, or an alternative explanation might be that butorphanol administration caused muscle relaxation and decreased carbon dioxide production in both treatment groups at the second sample period.

Healthy animals are often able to deal with physiologic disturbances by compensatory mechanisms. Fit animals may metabolize and excrete lactic acid produced during exertion if additional stresses are not created during the immobilization, such as postural changes that cause decreased oxygenation and tissue perfusion.[3,11] Recumbent rhinoceros that received butorphanol in the dart had lower median lactates at sample period 1 compared with those that did not receive butorphanol. In human patients, initial lactate levels and the amount of decrease over time were significantly associated with morbidity and mortality.[8] Methods to minimize lactic acid production would decrease risk of complications in other species as well.

The primary goal of the study was to determine the clinical outcome of butorphanol administered in darts or postimmobilization in free-ranging white rhinoceros and the potential effects on the cardiorespiratory system. This comparison suggests that initial administration of butorphanol in the dart seemed to decrease some of the metabolic disturbances associated with capture by keeping rhinoceros standing to facilitate ventila-

tion and decrease production of lactic acid. There may be situations when it is better for rhinoceros to become recumbent before handling in the field. Therefore, using butorphanol i.v. after they are immobilized may be a more appropriate choice for staff safety while still receiving some of the benefits of improved values such as decreased heart rate, lactate, and $PaCO_2$, with a tendency toward increased SaO_2.

In summary, the data suggest that butorphanol may be beneficial in improving metabolic parameters in immobilized free-ranging white rhinoceros. The hypothesis proposed is that the beneficial effect of butorphanol administered to white rhinoceros is based on a change in immobilization level rather than a direct antagonism of μ2-mediated receptor depression based on the lack of evidence of improved respiratory parameters. This conclusion is based on the persistence of hypoxemia in rhinoceros given these drug combinations, although standing rhinoceros seemed to have improved values overall. Early administration in the dart drug combination seems to have advantages over administration after immobilization in reducing lactate and improving pH and other potential contributing factors to metabolic imbalances that can lead to complications such as acidosis and capture myopathy. However, further research is needed to understand the mechanisms and other factors by which butorphanol exerts its effects in opioid-immobilized white rhinoceros.

Acknowledgments: The authors thank the staff of the Kruger National Park Veterinary Wildlife Services for support and assistance with this study, with a special thanks to Charlie Thompson and Grant Knight for skilled helicopter flying. The study was partially supported by a grant from the International Rhino Foundation and by financial support from the Palm Beach Zoo and Kruger National Park Veterinary Wildlife Services.

LITERATURE CITED

1. Bush, M., J. P. Raath, D. Grobler, and L. Klein. 2004. Severe hypoxaemia in field-anesthetised white rhinoceroses (*Ceratotherium simum*) and effects of using tracheal insufflations of oxygen. J. S. Afr. Vet. Assoc. 72: 79–84.

2. Citino, S. B., and M. R. Bush. 2007. Reference cardiopulmonary physiologic parameters for standing, unrestrained white rhinoceroses (*Ceratotherium simum*). J. Zoo Wildl. Med. 38: 375–379.

3. Gleed, R. D., and A. Dobson. 1988. Improvement in arterial oxygen tension with change in posture in anaesthetized horses. Res. Vet. Sci. 44: 255–259.

4. Hattingh, J., and C. M. Knox. 1994. Arterial blood pressure and blood gas composition of white rhinoceroses under etorphine anaesthesia. S. Afr. J. Wildl. Res. 24: 12–14.

5. Hawkinson, J. E., M. Acosta-Burruel, and S. A. Espitia. 2000. Opioid activity profiles indicate similarities between the nociceptin/orphanin FQ and opioid receptors. Eur. J. Pharmacol. 389: 107–14.

6. Hofmeyr, M. S. 2006. Black and white rhinoceros capture in the wild. Proc. North Am. Vet. Conf. 20: 1767–1770.

7. Hoskins, P. J., and G. W. Hanks. 1991. Opioid agonist-antagonist drugs in acute and chronic pain states. Drugs 41: 326–344.

8. Husain, F. A., M. J. Martin, P. S. Mullenix, S. R. Steele, and D. C. Elliott. 2003. Serum lactate and base deficit as predictors of mortality and morbidity. Am. J. Surg. 185: 485–491.

9. Isaza, R., B. J. Behnke, J. K. Bailey, P. McDonough, N. C. Gonzalez, and D. C. Poole. 2003. Arterial blood gas control in the upright versus recumbent Asian elephant. Respir. Physiol. Neurobiol. 134: 169–176.

10. Kock, M. D., P. Morkel, M. Atkinson, and C. Foggin. 1995. Chemical immobilization of free-ranging white rhinoceros (*Ceratotherium simum*) in Hwange and Matobo national parks, Zimbabwe, using combination of etorphine (M99), fentanyl, and detomidine. J. Zoo Wildl. Med. 26: 207–219.

11. Morkel, P. V., R. W. Radcliffe, M. Jago, P. DuPreez, M. J. B. F. Flaminio, D. V. Nydam, A. Taft, D. Lain, 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 insufflations: a preliminary report. J. Wildl. Dis. 46: 236–245.

12. 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: 22–30.

13. Pereira, F. G., S. A. Greene, R. Keegan, A. Tibary, and M. M. McEwen. 2005. Cardiovascular effects of butorphanol in isoflurane-anesthetized alpacas. Vet. Anaesth. Anal. 32: 8–9.

14. Radcliffe, R. W., and P. Morkel. 2007. Rhinoceroses. *In:* West, G., D. Heard, and N. Caulkett (eds.). Zoo Animal and Wildlife Immobilization and Anesthesia. Blackwell Publishing, Ames, Iowa. Pp. 543–566.

15. Vivian, J. A., M. B. DeYoung, T. L. Sumpter, J. R. Traynor, J. W. Lewis, and J. H. Woods. 1999. kappa-Opioid receptor effects of butorphanol in rhesus monkeys. J. Pharmacol. Exp. Ther. 290: 259–265.

16. 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 11 March 2012