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EVALUATION OF CARDIORESPIRATORY, BLOOD GAS, AND LACTATE VALUES DURING EXTENDED IMMOBILIZATION OF WHITE RHINOCEROS (*CERATOTHERIUM SIMUM*)

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Abstract: Ten white rhinoceros (*Ceratotherium simum*) were immobilized for a total of 13 procedures in holding facilities in Kruger National Park using etorphine, azaperone, and hyaluronidase to assess the effect of extended immobilization on serial cardiorespiratory, blood gas, and lactate values. Butorphanol was administered intravenously following initial blood collection and physiologic assessment (t = 0). Respiratory and cardiovascular parameters, body temperature, and arterial blood gases were monitored at 10-min intervals for a total of 100 min. Initial parameters at the time of recumbency revealed severe hypoxemia, hypercapnia, tachycardia, an increased alveolar-arterial (A-a) gradient, and mildly elevated lactate levels. At 10 min and 20 min, there were significant ($P < 0.05$) changes in the following physiologic parameters: heart rate decreased [96 and 80 beats/min, respectively, vs. 120 beats/min], arterial partial pressure of oxygen (PaO_2) increased [48 and 45 mm Hg, respectively vs. 30 mm Hg], arterial hemoglobin oxygen saturation increased [79% and 74%, respectively, vs. 47%], A-a gradient decreased [29.13 and 30.00 mm Hg, respectively, vs. 49.19 mm Hg], and respiratory rate decreased [5 and 5 breaths/min vs. 7 breaths/min]. Blood lactate levels also decreased from 2.54 mM/L to 1.50 and 0.89 mM/L, respectively. Despite initial improvements in blood oxygen levels at t = 10 and 20 min, the rhinoceros remained severely hypoxemic for the remainder of the procedure (median $PaO_2 = 50.5$ mm Hg, 95% confidence interval, 43.8–58.1). Median values for respiratory rate (5 breaths/min) and arterial partial pressure of carbon dioxide ($PaCO_2$; 68.5 mm Hg) did not change significantly for the remaining 80 min. Median lactate, base excess, bicarbonate, and pH values improved between 20 and 100 min despite the persistent hypercapnia, indicating that the animals adequately compensated for respiratory and lactic acidosis. White rhinoceros were immobilized for 100 min with no negative effects, a desirable outcome if procedures require extended chemical immobilization without oxygen supplementation.

Key words: Blood gas, butorphanol, cardiorespiratory, *Ceratotherium simum*, white rhinoceros.

INTRODUCTION

Free-ranging white rhinoceros (*Ceratotherium simum*) are routinely immobilized with etorphine, a potent opioid, combined with the butyrophenone tranquilizer azaperone for medical and management procedures.[28] Tachycardia, hypopnea, hypoxemia, and hypercapnia with respiratory and metabolic acidosis are well-documented side effects of the drug combination in this species.[2,4,17,28] These potentially fatal complications are managed by minimizing the time an animal is kept immobilized before a complete opioid antagonist is administered.[1] Partial opioid antagonists, including nalorphine and diprenorphine; nasal or tracheal oxygen insufflation; and respiratory stimulants such as doxapram have also been used to counteract these negative effects with limited and variable degrees of success.[1,2,23,24] At times there is a requirement to keep an animal immobilized in the field for a prolonged period of time (≥20 min), such as during the treatment of

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injuries caused by poaching, including the removal of snares and bullet wounds.[28] Frequently these operations are helicopter based and are performed without the advantages of inhalation anesthesia, oxygen insufflation, or mechanical ventilation.[2,28] Etorphine, the primary immobilizing agent, is a μ, κ, and Δ opioid peptide (MOP, KOP, and DOP, respectively) receptor agonist.[31] Butorphanol, a synthetic opioid reported to have KOP receptor agonist and MOP receptor antagonist effects, has anecdotally been used to improve ventilation in opioid-immobilized white rhinoceros.[23,31] The objective of this descriptive study was to record and evaluate the cardiorespiratory, blood gas, and lactate values in white rhinoceros immobilized for an extended time period (100 min) with no oxygen support and a single dose of butorphanol. The lack of a control group in this clinical study prevents the rendering of definitive conclusions about the effects of butorphanol; however, it does raise a number of potential research questions to be pursued in future analytical studies.

MATERIALS AND METHODS

Study area and sample population

The study animals were white rhinoceros captured in Kruger National Park (24°59′44.50″S, 31°35′11.17″E; altitude 317 m), South Africa, and placed into holding facilities for management purposes. The management and immobilization of the rhinoceros were conducted according to the South African Parks Standard Operating Procedures for the Capture, Transportation and Maintenance in Holding Facilities of Wildlife. These animals were part of another study that required a prolonged period of immobilization.

Ten animals were used in this descriptive study; three individuals were immobilized twice on separate occasions. Rhinoceros ranged in age from 3.5 to 15 yr and included four males and six females. Prior to being included in this trial, all animals had adapted to captivity and were eating and defecating normally. Animals were deemed healthy based on behavior, dietary intake, body condition, and physical examination.

Each rhinoceros received a combination of etorphine (9.8 mg/ml; Novartis, Kempton Park 1619, South Africa), azaperone (40 mg/ml; Janssen Pharmaceutical Ltd., Halfway House 1685, South Africa), and hyaluronidase (5,000 IU/vial; Kyron Laboratories, Benrose 2011, South Africa) delivered into the muscles of the nuchal hump remotely using a 3.0-ml plastic dart with a 60-mm uncollared needle propelled by a compressed air rifle (DAN-INJECT, International S.A., Skukuza 1350, South Africa). Doses were based on standardized age categories: 3 to 4 years = 2.5 mg etorphine, 20 mg azaperone, and 5,000 IU hyaluronidase; 4 to 5 years = 3.0 mg etorphine, 40 mg azaperone, and 5,000 IU hyaluronidase; and ≥5 years = 4 mg etorphine, 40 mg azaperone, and 5,000 IU hyaluronidase. Darting took place early in the morning prior to feeding or cleaning of enclosures to ensure minimal disturbance or stimulation of the animals.

All animals were recumbent within 10 min after darting and were blindfolded as soon as they could be safely approached and placed in sternal recumbency. Each rhinoceros's body position was alternated between sternal and lateral recumbency at 20-min intervals to ensure adequate ventilation of both lung fields and perfusion of limbs, respectively.

At t = 0, once the rhinoceros were handled for the first time, an initial blood sample was obtained. Butorphanol (50 mg/ml; Kyron Laboratories) was administered intravenously at 10 times the etorphine dose (mg) into an auricular vein immediately following the collection of samples and assessment of cardiorespiratory parameters at t = 0. Arterial blood samples were collected, and heart rate, respiratory rate, and rectal temperature were measured every 10 min starting at t = 0, for a total duration of 100 min. Initial handling of recumbent rhinoceros was designated time 0 min (t = 0). The first sample collected after the administration of butorphanol was obtained at 10 min (t = 10). This single butorphanol dose was selected since it is commonly used in field immobilization of free-ranging white rhinoceros and because subjective results suggest it improves cardiorespiratory functions.[17]

At the end of the procedure, naltrexone (40 mg/ml; Kyron Laboratories) was administered intravenously at 33.3 to 57 times the etorphine dose (mg), and the animal was kept under observation until it had fully recovered.

Sample collection and assays

Arterial samples were collected from the medial auricular artery in a 1-ml heparinized syringe and 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 oxygen (PaO_2), arterial partial pres-

Table 1. Mean, standard deviation, median, interquartile range, and number of observations for each cardiopulmonary parameter at sampling periods 0, 10, and 20 min.[a]

Sample time (min)	Distribution	Respiratory rate (breaths/min)	Heart rate (beats/min)	Rectal temperature (°C)	BE_{ecf} (mmol/L)	HCO_3^- (mm Hg)
	Mean	7.62	121.46	36.60	9.46	35.25
	SD	2.22	16.52	0.76	3.36	3.61
	Median	7.00	120.00	36.70	8.00	33.50
	IQR	6.00, 8.00	112.00, 130.00	36.15, 37.09	7.00, 12.00	32.70, 37.40
	n	13	13	12	13	13
10	Mean	6.31	86.31	36.71	9.31	35.52
	SD	2.50	21.62	0.84	4.63	4.39
	Median	5.00	96.00	36.75	9.00	35.20
	IQR	5.00, 7.00	68.00, 100.00	36.25, 37.40	5.00, 14.00	31.70, 39.90
	n	13	13	12	13	13
20	Mean	5.92	80.31	36.64	10.15	36.12
	SD	2.72	16.60	0.75	4.88	4.73
	Median	5.00	80.00	36.60	11.00	37.40
	IQR	4.00, 8.00	68.00, 94.00	36.40, 37.20	7.00, 15.00	33.10, 40.30
	n	13	13	13	13	13

[a] IQR indicates interquartile range (25th–75th percentile); BE_{ecf}, base excess; HCO_3^-, bicarbonate; SaO_2, arterial hemoglobin oxygen saturation; PaO_2, arterial partial pressure of oxygen' $PaCO_2$, arterial partial pressure of carbon dioxide; A-a gradient, alveolar – arterial gradient.

sure of carbon dioxide ($PaCO_2$), pH, and lactate were measured by the machine; PaO_2, $PaCO_2$, and pH were corrected for body temperature. Base excess (BE_{ecf}), bicarbonate (HCO_3^-), and arterial hemoglobin oxygen saturation (SaO_2) were values calculated by the blood gas analyzer. Heart rate was determined by auscultation of the heart or palpation of the medial auricular artery. Respiratory rate was measured by visual assessment of thoracic-abdominal excursions and air movement at the nares. The Alveolar – arterial (A-a) oxygen gradient was calculated using the formula $FIo_2(Pb\text{-}P_{H2O}) - Paco_2 - Pao_2$, as reported by Meyer et al.[16] A measured mean barometric pressure (Pb) of 739 mm Hg and an inspired oxygen fraction (FIo_2) of 21 mm Hg were used in all calculations. The water vapor pressure of saturated air in the alveoli (P_{H2O}) was calculated as $4.58 \exp [(17.27T_b)/(237.3 + T_b)$. Body temperature ($T_b$) was measured by placing a thermometer deep into the rectum against the rectal wall. It was assumed that alveolar partial pressure of carbon dioxide was equilibrated with $PaCO_2$.[16]

Data analysis

STATA (Stata Statistical Software: Release 11, College Station, Texas 77840, USA) was used for the statistical analysis. Means, standard deviations, medians, and first (Q1) and third (Q3) quartile were calculated for descriptive purposes for rhinoceros at different sampling points (10-min intervals). As a result of the relatively small sample size obtained for this study, nonparametric statistical tests were used to compare median values at different sampling points (over 100 min). Initially, the data were screened using the Kruskal–Wallis test to assess if median values for different cardiorespiratory, blood gas, A-a gradient, and lactate values differed over sampling points (over 100 min). Secondly, a pairwise comparison of adjacent intervals (i.e., 0 to 10, 30 to 40, 70 to 80 min, etc.) was conducted to assess differences in median cardiorespiratory, blood gas, A-a gradient, and lactate values within a 10-min period using the Wilcoxon rank sum test. All sampling points were compared to the baseline values at $t = 0$ (before the administration of butorphanol). To account for repeated measurements (lack of independence among samples taken from the same rhinoceros at different sample points and the three rhinoceros sampled twice), a mixed linear regression model using ranks was used to evaluate the effect of time on the cardiorespiratory, blood gas, A-a gradient, and lactate values over time, including the sample intervals (every 10 min), as a fixed effect and using $t = 0$ as the reference value. Based on the initial results and distribution of data (indicating that most clinically relevant changes in cardiorespiratory, blood gas, A-a gradient, and lactate values occurred during the first 20 min and then tended to stabilize), the analysis (mixed linear regression using ranks as described above) was repeated in order to formally assess changes on cardiorespi-

Table 1. Extended.

SaO_2 (%)	Lactate (mmol/L)	Corrected pH	Corrected $PaCO_2$ (mm Hg)	Corrected PaO_2 (mm Hg)	A-a gradient (mm Hg)
51.46	2.88	7.34	65.33	30.83	49.35
18.13	1.72	0.04	11.71	9.36	10.26
47.00	2.48	7.34	60.95	30.00	49.19
44.00, 64.00	1.87, 3.46	7.33, 7.36	58.85, 68.45	25.00, 37.50	39.59, 58.95
13	13	12	12	12	12
74.77	2.10	7.32	69.05	47.31	29.07
17.18	1.87	0.04	10.03	11.00	6.95
79.00	1.50	7.32	64.80	48.00	29.13
76.00, 82.00	1.09, 1.91	7.31, 7.35	60.90, 76.10	42.00, 54.00	26.90, 33.28
13	13	13	13	13	13
73.92	1.13	7.33	68.89	47.00	29.53
14.44	0.71	0.04	9.04	12.63	13.82
74.00	0.89	7.34	68.40	45.00	30.00
66.00, 84.00	0.60, 1.44	7.29, 7.36	67.70, 70.80	39.00, 53.00	23.04, 32.83
13	12	13	13	13	13

ratory, blood gas, A-a gradient, and lactate values after 20 min using t = 20 as the reference value. To summarize the data for the last 80 min of the immobilization procedure (between 20 and 100 min), the bootstrap method was used to obtain the median (and median 95% confidence interval [CI]) for each parameter. Box plot graphs were used to present the distribution of data for selected parameters over the 100-min period. Statistical significance was set at $P < 0.05$ for all statistical tests.

RESULTS

Median cardiorespiratory values for rhinoceros at initial sampling (t = 0) were as follows: respiratory rate = 7 breaths per min (breaths/min), PaO_2 = 30 mm Hg, SaO_2 = 47%, $PaCO_2$ = 60.95 mm Hg, A-a gradient = 49.19, mm Hg and heart rate = 120 beats/min. Median arterial blood pH was 7.34, BE_{ecf} = 8 mM/L, HCO_3^- = 33.5 mM/L, lactate = 2.48 mM/L, and rectal temperature = 36.7°C (Table 1). Rhinoceros also initially exhibited muscle tremors and limb rigidity. The mean induction time from darting to recumbency for all rhinoceros in the study was 5.71 min (95% CI, 4.69–6.72).

At t = 10 and t = 20 there were a number of statistically significant changes in median values of physiologic parameters when compared to t = 0 (Table 1). Subjective observations also showed improved muscle relaxation, with a reduction in tremors. PaO_2 (48 and 45 mm Hg, respectively) and SaO_2 (79% and 74%, respectively) both increased significantly at t = 10 and t = 20 min ($P < 0.0001$), and A-a gradient (29.13 and 30.00 mm Hg, respectively) decreased significantly at the same time points ($P < 0.001$). Heart rate decreased significantly to 96 beats/min at 10 min and 80 beats/min at 20 min, compared to 120 beats/min at t = 0 ($P < 0.001$). Compared to values at t = 0 (2.48 mM/L), lactate levels were lower at t = 10 (1.50 mM/L, $P = 0.019$) and t = 20 (0.89 mM/L, $P < 0.001$). Respiratory rate decreased from 7 breaths/min at t = 0 to 5 breaths/min at t = 10 ($P = 0.005$) and remained at 5 breaths/min at t = 20 ($P < 0.0001$). At t = 10, a significant difference was observed in median pH (7.32) when compared to the value at t = 0 (7.34). There were no significant changes at t = 10 and t = 20 in median rectal temperatures, BE_{ecf}, HCO_3^-, and $PaCO_2$ compared to the corresponding values at t = 0.

During the latter periods of immobilization (20–100 min), median values for respiratory rate and $PaCO_2$ (Fig. 1) did not change significantly, although both SaO_2 and PaO_2 remained at higher levels compared to the values at t = 0 (Fig. 2). Compared to t = 20 (74%), SaO_2 was significantly ($P < 0.05$) different at t = 50, 60, 70, 90, and 100, with median oxygen saturation levels at 88%, 89%, 84%, 91%, and 85%, respectively. PaO_2 values followed the same trend as SaO_2. PaO_2 was significantly ($P < 0.05$) different at t = 50, 60, 90, and 100, with median values at 57, 61, 59, and 52 mm Hg, respectively, compared to values at t = 20 (45 mm Hg). A-a gradients at t = 50, 60, and 90 min were significantly ($P < 0.05$) different from t = 20 (30 mm Hg), with values of 20.37, 20.98, and 20.07 mm Hg, respectively. There was

Table 2. Summary distribution (mean, standard deviation, minimum, 25th percentile [Q1], median, 75th percentile [Q3], maximum, 95% confidence interval [CI] for the median, and number of observations) for each cardiopulmonary parameter over the last 80 min (between 20 and 100 min) of the immobilization.[a]

Estimate	Respiratory rate (breaths/min)	Heart rate (beats/min)	Rectal temperature (°C)	BE_{ecf} (mmol/L)	HCO_3^- (mm Hg)
Mean	5.60	71.40	36.50	13.60	38.77
Standard deviation	2.45	15.53	0.77	4.62	4.28
Minimum	2.00	36.00	35.00	1.00	25.90
Q1	4.00	60.00	36.00	9.00	35.10
Median	5.00	71.00	36.40	14.00	39.60
Q3	6.00	80.00	36.90	17.00	42.20
Maximum	16.00	114.00	38.30	22.00	47.40
Median 95% CI[b]	3.7–6.3	64.1–79.9	36.1–36.7	9.3–18.7	35.8–43.4
n	94	94	94	93	93

[a] BE_{ecf}, base excess; HCO_3^-, bicarbonate; SaO_2, arterial hemoglobin oxygen saturation; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; A-a gradient, alveolar – arterial gradient.

[b] The median 95% CIs were obtained using the bootstrap method to account for lack of independence due to repeated measurement in the same rhinoceros over time.

an overall decreasing trend in heart rate, with significant differences observed at t = 50 and t = 100 (72 and 62 beats/min, respectively; $P < 0.003$). Median rectal temperature decreased from 36.7°C (t = 20) to 36.4°C (t = 100), although this change was not statistically significant ($P = 0.07$).

Median pH values improved from 7.34 (t = 20) to 7.37 (t = 90) ($P = 0.001$). Other significant changes in acid–base status between 20 and 100 min included increases in BE_{ecf} and HCO_3^- and a decrease in lactate. BE_{ecf} continued to rise after t = 20 (11 mM/L), with significant differences observed at t = 40 and beyond (17 and 16 mM/L at t = 80 and t = 100, respectively; $P \leq 0.015$). Bicarbonate ions also increased over time, with median values at t = 50 and later (41.35 mM/L at t = 100) significantly ($P \leq 0.011$) higher than values at t = 20 (37.4 mM/L). Lactate values after 20 min continued decreasing, and median values were significantly different at t = 80 (0.68 mM/L; $P = 0.033$), t = 90 (0.46 mM/L; $P = 0.023$), and t = 100 (0.80 mM/L; $P = 0.006$), compared to the value at t = 20 (0.89 mM/L) (Fig. 3). A summary distribution for each cardiopulmonary parameter over the last 80 min of immobilization is shown in Table 2.

DISCUSSION

The purpose of this study was to evaluate the cardiorespiratory, blood gas, and lactate values in white rhinoceros immobilized for a prolonged period of time with a single dose of butorphanol administered intravenously and in the absence of supplementary oxygen. Historically, white rhinoceros have only been kept immobilized for short time periods (≤20 min) as a result of the perceived

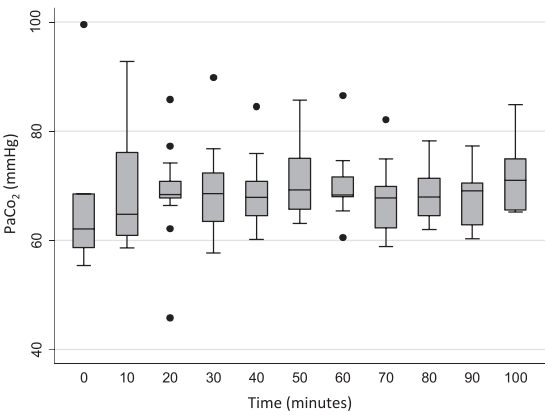

Figure 1. Distribution of $PaCO_2$ values over a 100-min immobilization of white rhinoceros.

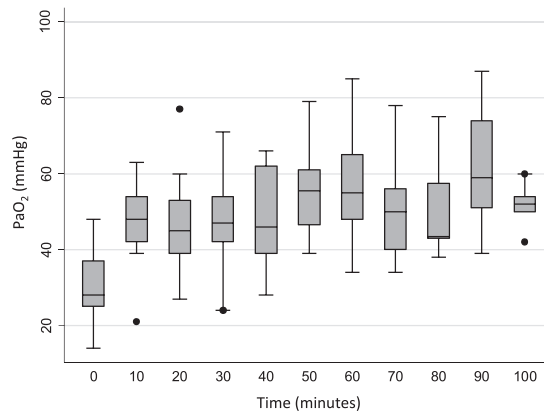

Figure 2. Distribution of PaO_2 values over a 100-min immobilization of white rhinoceros.

Table 2. Extended.

SaO_2 (%)	Lactate (mmol/L)	Corrected pH	Corrected PaO_2 (mm Hg)	Corrected $PaCO_2$ (mm Hg)	A-a gradient (mm Hg)
80.02	1.06	7.35	51.90	69.20	24.70
12.40	0.78	0.04	13.30	7.10	10.40
35.00	0.30	7.25	24.00	45.80	0.16
74.00	0.50	7.33	42.50	65.20	17.30
83.00	0.90	7.36	50.50	68.50	25.60
89.00	1.30	7.38	60.00	72.20	32.80
96.00	4.70	7.41	87.00	89.80	64.10
76.9–89.1	0.6–1.2	7.3–7.4	43.8–58.1	65.3–71.7	21.2–30.0
93	92	92	92	92	91

threats associated with severe opioid-induced respiratory depression.[1,22]

The initial observations of hypopnea, hypoxemia, hypercapnia, and tachycardia are consistent with other reports of immobilized rhinoceros.[2,4,17,28] Hypoxemia occurs when $PaO_2 \leq 80$ mm Hg; levels reaching 50–60 mm Hg usually require corrective action in an anesthetized animal.[25] The elevated $PaCO_2$ (median $PaCO_2 = 60.95$; normal range = 44.4–53.7 mm Hg[4]) at the first sampling period indicated that the hypoxemia (median $PaO_2 = 30$ mm Hg; normal range = 90.2–108.6 mm Hg[4]) was, in part, caused by hypoventilation.[13,29] Since the PCO_2 values of alveolar gas and arterial blood in healthy individuals are almost identical, changes in $PaCO_2$ are indicative of variations in alveolar ventilation, with hypoventilation resulting in increased arterial carbon dioxide values.[29] As alveolar ventilation decreases and $PaCO_2$ increases, there will be a corresponding drop in PaO_2 levels as rates of alveolar oxygen replenishment are reduced. Hypoventilation is a pronounced side effect associated with the administration of opioids and is mediated by the activation of MOP, KOP, and DOP receptors, reducing the sensitivity of carotid and aortic bodies to hypoxemia and, more significantly, the sensitivity of brainstem chemosensory neurons to increasing carbon dioxide levels.[15,18] In addition, opioids have depressant effects on respiratory neurons in the brainstem, causing alterations to rhythmogenesis, with resulting hypopnea.[31] Opioids can further compromise ventilation through increased chest wall rigidity, which limits changes in intrathoracic pressure, and the expansion and return to rest of lungs in the immobilized animal.[22] Reduced upper airway patency following the administration of opioids can further compromise alveolar ventilation because of increased resistance to air movements through the respiratory tree.[28,31]

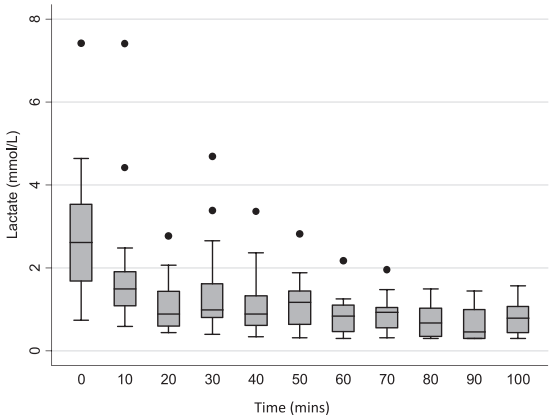

Figure 3. Distribution of lactate values over a 100-min immobilization of white rhinoceros.

The high A-a gradient (median A-a gradient = 49.19 mm Hg; normal equine A-a gradient = approximately 10 mm Hg[5]) suggests that ventilation/perfusion mismatching (V/Q ratio), a physiologic right-to-left shunt, and diffusion impairment may have also contributed to the low oxygen tension.[11,29] A lower V/Q ratio (proportion of air to blood reaching an alveoli) for a particular lung area will impair pulmonary gas exchange and result in a lower PaO_2. As a result of the "S" shape of the oxygen–hemoglobin dissociation curve, areas of high V/Q ratios have limited effect on arterial PaO_2.[29] A shunt (V/Q ratio = 0) occurs when blood flows past unventilated alveoli or in pulmonary tissue not associated with alveoli, resulting in no gaseous exchange. This unoxygenated blood flows from the arterial to the venous pulmonary circulation, leading to a lower PaO_2.[15,29] Opioids decrease PaO_2 through reduced

alveolar ventilation and by decreasing pulmonary perfusion. Pulmonary vasoconstriction occurs with opioids because of both hypoxia and direct effects on vasculature.[16] A decreased V/Q ratio, including shunts, will also impair carbon dioxide excretion; normally this does not result in an increased arterial carbon dioxide tension, since as $PaCO_2$ rises, respiration is stimulated. However, in the immobilized animal, because of the opioid-induced respiratory inhibition, an increase in $PaCO_2$ would be expected. The impact of immobilizing drugs used in rhinoceros on the hypoxic pulmonary vasomotor response is unknown, although injectable anaesthetics, including narcotics, barbiturates, and benzodiazepines, examined in domestic animals do not have any detectable effect.[15,29] Large anesthetized recumbent animals are subject to ventilation–perfusion disparities due to lung compression by body mass and alterations to tidal volume from the abdominal organs impinging on the diaphragm.[19,23] Diffusion of oxygen may be impaired by an increase in the physical separation between alveolar gas and pulmonary capillary blood (caused by interstitial or pulmonary edema) and a shortened pulmonary transit time of blood. Since the rhinoceros in this study were clinically healthy, it is believed they did not have any lung pathology that may have reduced diffusion. However, it has been demonstrated in goats that etorphine causes an increase in the A-a gradient due to pulmonary hypertension, and it is proposed that this may result in pulmonary edema, which impairs the diffusion of oxygen (Meyer, pers. comm.). It may also reduce the time for gaseous exchange because of a reduced blood transit time through the alveolar capillaries.

Arterial oxygen levels (PaO_2 and SaO_2) improved markedly in the first 10 min following the administration of butorphanol in the immobilized white rhinoceros. Significant differences in these variables did not occur again until later in the immobilization period ($t = 50$ and beyond) and were not as large as the initial change. These findings suggest that the initial improvement in arterial oxygen tension was due to the administration of butorphanol rather than to an effect of time reducing the immobilizing drug effects through metabolism and redistribution, as likely occurred later in the immobilization (Tables 1, 2). Improved alveolar ventilation would increase PaO_2 levels; however, there was no evidence to indicate an increase in ventilation, since $PaCO_2$ values did not change significantly during the extended immobilization.[29] Increased PaO_2 without concurrent changes in $PaCO_2$ indicates that etorphine-induced respiratory depression was not antagonized by the administration of butorphanol. The significant reduction in the A-a gradient from $t = 0$ to $t = 10$ may also have contributed to the increase in PaO_2 through potential improvements in the V/Q ratio, shunt fraction, diffusion of oxygen, or various combinations of all three.

Although the results of these clinical observations do not elucidate the mechanism responsible for the improved PaO_2, a number of possibilities are proposed. Butorphanol is reported to reduce muscle rigidity and trembling of limbs in rhinoceros associated with the administration of etorphine, which would reduce tissue oxygen requirements.[23] Decreased tissue oxygen demands, without changes in pulmonary gaseous exchange, can lead to increased blood oxygen levels.[15] Azaperone, included in the initial immobilizing drug combination, may also have caused muscle relaxation, as maximum activity of this drug is reached within 20 to 30 min after administration.[1] However, it has been observed by the author (PB) during capture of large numbers of rhinoceros ($\geq$500) with etorphine and azaperone that muscle tremors and rigidity persist through the immobilization period if butorphanol is not administered. Recent studies in boma-confined white rhinoceros immobilized with etorphine and azaperone without butorphanol administration, in which muscle tremors persisted, did not show an increase in PaO_2 over 20 min.[11] As a partial mixed opioid agonist–antagonist, butorphanol may also relieve muscle rigidity, which impairs the movement of the thoracic wall and diminishes upper airway patency.[2,21,28] It could also counteract etorphine-associated pulmonary vasoconstriction, resulting in improved pulmonary gas exchange and, hence, blood oxygenation.[16]

Despite persistently high $PaCO_2$ levels, respiratory rate decreased significantly in the first 10 min and then remained at this level for the remaining 90 min. This may have been due to ongoing drug-induced respiratory depression by the initial immobilizing drugs or the KOP receptor agonist effects of butorphanol.[26] However, the decrease in respiratory rate was associated with improved blood oxygen values. Possible explanations for this change in PaO_2 include decreased tissue metabolism and oxygen consumption, an increase in tidal volume with a fractional decrease in alveolar dead space ventilation, an improvement in the A-a gradient, or various combinations of all three.

In the exercising animal, increased lactate values are used as a measure of anaerobic metabolism due to hypoxia or tissue hypoperfusion. The highest median lactate value (2.48 mM/L) occurred at t = 0 but was lower than that observed in field-immobilized white rhinoceros.[17] This is not unexpected, as free-ranging animals are usually darted from a helicopter and experience high levels of muscle activity prior to and during the immobilization induction phase compared to the boma-confined study animals.[19] Normal resting lactate values in white rhinoceros are not available in the literature; however, values for horses (0.70–2.85 mM/L) suggest the lactate levels in these rhinoceros were resting or slightly elevated.[21] An initial increase in lactate production may have occurred as a result of opioid-induced localized muscle activity and limb rigidity (tremors) combined with hypoxemia during the induction phase.[1] A decrease in anaerobic metabolism and muscle activity in the immobilized animal would result in progressively decreasing lactate levels.

Despite a persistent hypercapnia, lactate levels and other acid–base parameters improved over time. The initial moderate acidosis improved as a result of increased BE_{ecf} and HCO_3^- and decreased lactic acid (Fig. 3; Tables 1, 2). These results indicate that the improvement in acid–base status was metabolic in origin rather than dependent on respiratory compensatory mechanisms.

The rhinoceros in this study were tachycardic at t = 0 despite minimal exertion associated with darting in a confined holding space. Etorphine is reported to cause both tachycardia and bradycardia depending on dose, species, and other concurrently administered drugs.[3,12] Pronounced tachycardia and increased blood pressure have been reported in elephants after administration of etorphine.[7,10] At t = 20, the median heart rate in rhinoceros was reduced by approximately one-third from the initial tachycardia (median 120 beats/min). This reduction may be due to a partially reversed hypoxemic vasodilator effect associated with increases in PaO_2 and SaO_2 or a decline in the sympathetic response to hypoxia.[8,9] Another possibility is a direct opioid receptor-mediated effect on the heart.[6] A more complete understanding of the observed heart rate changes would require measures of cardiac output, stroke volume, and total peripheral resistance. The α_1-adrenoceptor antagonist activity of azaperone on peripheral vasculature should also be taken into account.

There is a paucity of literature regarding the effects of butorphanol on the cardiovascular system. In humans, butorphanol reduces tachycardia in patients under the influence of cocaine; the explanation for this observation has not been elucidated.[30]

The underlying mechanism for changes in PaO_2, SaO_2, and respiratory and heart rates during the first 20 min requires further investigation. Although the timing of observed changes in this report indicates that butorphanol may have contributed to these effects, interpretation is limited by the lack of a control group (i.e., animals to which no butorphanol was administered), which was not included because of the requirements of a concurrent study using these individual animals. Anecdotal observations suggest butorphanol improves immobilization quality and physiologic parameters in white rhinoceros.[22] However, the specific behavioral, pharmacologic, and therapeutic effects of this mixed opioid agonist–antagonist are not clearly defined in complex biological systems. The clinical effects of butorphanol in immobilized rhinoceros are further complicated by the presence of etorphine, a potent pure agonist at all three opioid peptide receptors.[31] In humans, the actions of butorphanol are similar to those of pentazocine, which does not antagonize the respiratory depression produced by morphine. In postoperative patients, 2 to 3 mg of butorphanol produced a respiratory depression equivalent to that of 10 mg of morphine.[31] Butorphanol administered to rhesus monkeys resulted in a dose-dependent decrease in respiratory minute volume and behavioral effects consistent with MOP receptor activity, which overrides KOP receptor-mediated actions.[27,30] The receptor binding profile of butorphanol also varies between species, and the precise mechanism of action is not fully elucidated. Pharmacologic effects in rhesus monkeys and pigeons are produced through MOP receptors, compared to both MOP and KOP receptors in laboratory rodents.[30] It has previously been reported[28] that butorphanol did not result in any benefits to ventilation in immobilized white rhinoceros. However, the effects of butorphanol may have been dampened in this study by the addition of detomidine to the etorphine and azaperone combination. Detomidine, an α_2-agonist, can cause significant negative respiratory effects, compounding those of the opioids.[28]

As a result of the severe hypoxemia that occurs in opioid-immobilized white rhinoceros, it has been suggested that oxygen supplementation

should be routinely used; however, this can be difficult to accomplish. Under extensive conditions, animals are frequently immobilized many kilometers from a home base with limited personnel and equipment associated with helicopter capture. Orotracheal intubation can be demanding in white rhinoceros because of the size of the head and the muscle rigidity associated with the use of etorphine, which makes it difficult to open the mouth.[2] Intermittent positive pressure ventilation requires the placement of a cuffed endotracheal tube and use of high-capacity ventilators or a demand valve connected to a large source of compressed air.[2] Oxygen supplementation into the trachea using an equine nasogastric tube passed through the nasal cavity has also been described.[2]

A recent study[11] has shown that the oxygen supplementation in white rhinoceros immobilized with etorphine and azaperone does not improve the resulting hypoxemia and causes further increases in $PaCO_2$ in animals that are already hypercapnic and a severe acidemia with worsening blood pH. It is hypothesized that these effects were due to increased intrapulmonary shunt fractions resulting in lung atelectasis. It is also possible that the high levels of hypercarbia, which result from increasing $PaCO_2$ levels in animals receiving oxygen, may depress central nervous system (CNS) respiratory control.[11] However, if butorphanol was administered prior to oxygen supplementation, hypoxemia was completely reversed, although neither $PaCO_2$ nor pH improved.[11] Similar results have been reported[2] in rhinoceros administered nalorphine (mixed opioid agonist–antagonist) or doxapram hydrochloride (CNS stimulant) prior to or during the intratracheal administration of supplementary oxygen to the level of the carina. Oxygen saturation increased to greater than 90%, although hypercapnia and academia persisted. In humans, supplemental oxygen exacerbates opioid-induced ventilatory depression, which may be due to decreased output of the peripheral and ventral medulla chemoreceptors, causing a reduced ventilation drive.[20]

CONCLUSION

Despite the relatively small sample size in this report ($n = 13$ white rhinoceros immobilizations), several statistically significant and clinically relevant changes occurred during the immobilization period. Initial severe hypoxemia in rhinoceros immobilized with etorphine and azaperone and administered a single i.v. dose of butorphanol (at 10 times the etorphine dose) at $t = 0$ improved during the first 20 min, as reflected by increased PaO_2 and SaO_2. However, the change in blood oxygen tension was limited, and animals remained hypoxic. Steadily declining lactate values indicate a lack of generalized anaerobic metabolism, which suggests that tissue oxygen delivery met metabolic demand or that metabolic rate and oxygen consumption was reduced during the first 20 min, or both.[14] $PaCO_2$ values did not change significantly, and hypercapnia persisted for the entire 100 min; however, during this time, acidosis was corrected by metabolic compensatory mechanisms. A well-designed study with controls is required to further investigate these initial results, which suggest that butorphanol may improve blood oxygen tension and provide some cardiovascular and acid–base support in immobilized rhinoceros. Factors such as body position and other potential confounders (e.g., body mass, age, drug dosages, and activity levels prior to drug administration) should also be considered. Observations indicate that healthy white rhinoceros immobilized with etorphine and azaperone and administered a single dose of butorphanol can tolerate prolonged periods (100 min) of hypoxemia and hypercapnia.

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