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EFFECTS OF A SUPPLEMENTAL ETORPHINE DOSE ON PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT IN IMMOBILIZED, BOMA-HABITUATED WHITE RHINOCEROS (*CERATOTHERIUM SIMUM*): A PRELIMINARY STUDY

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Abstract: The effects of etorphine on the pulmonary vascular system of white rhinoceros (*Ceratotherium simum*) have not been described and could play a role in the severe hypoxemia that develops after immobilization with etorphine-based drug combinations. Characterization of these effects requires measurement of pulmonary vascular pressures and cardiac output (CO). To refine a technique for pulmonary arterial catheterization, five boma-habituated white rhinoceros (three females and two males weighing 1,012–1,572 kg) were immobilized by remote injection with etorphine plus azaperone followed by butorphanol. This afforded the opportunity to perform a pilot study and acquire preliminary measurements of pulmonary arterial pressure (PAP) and CO before and after supplemental etorphine given intravenously. Ultrasonographic guidance was used to insert a sheath introducer into a linguofacial branch of a jugular vein. A 160-cm-long pulmonary artery catheter with a balloon and thermistor was then passed through the introducer and positioned with its tip in the pulmonary artery. It was not long enough to permit wedging for measurement of pulmonary artery occlusion pressure. Mean PAP was 35 mm Hg (minimum, maximum 32, 47 mm Hg) and increased ($P = 0.031$) by 83% (28, 106%) after supplemental etorphine. Thermodilution CO was 120 L/min (92, 145 L/min) and increased 27% (3, 43%) ($P = 0.031$). Heart rate was 100 (88, 112) beats/min and increased 20% (4, 45%) ($P = 0.031$), whereas arterial partial pressure of oxygen was 35 mm Hg (30, 94 mm Hg) and decreased 47% (20, 72%) ($P = 0.031$). The cardiovascular observations could result from etorphine-induced generalized sympathetic outflow, as has been reported in horses. Further studies of etorphine in isolation are needed to test this suggestion and to discern how the changes in pulmonary vascular pressures and blood flow might relate to hypoxemia in etorphine-immobilized white rhinoceros.

Key words: Cardiac output, *Ceratotherium simum*, etorphine, pulmonary artery catheter, pulmonary artery pressure, white rhinoceros.

INTRODUCTION

Life-threatening hypoxemia, hypercapnia, acidemia, and other serious physiological derangements are ubiquitous during chemical capture of wild white rhinoceros (*Ceratotherium simum*).[3,4,7,10,11] Chemical immobilization of this species in the wild is usually carried out by aerial darting with the potent μ opioid agonist etorphine, coadministered with a tranquilizer (e.g. azaperone) and subsequent partial reversal with a μ opioid receptor antagonist/κ opioid receptor agonist (e.g. butorphanol).[3,4,7,10,11] Extreme exertion during darting might contribute to the hypoxemia and other physiological perturbations. However, white rhinoceros exhibit severe hypoxemia, hypercapnia, respiratory acidemia, tachycardia, and systemic hypertension after darting with this combination of drugs in a boma where exertion is minimal.[2–4]

The above observation suggests that one or more of the drugs used in capture are primarily responsible for the hypoxemia and other perturbations. When given alone to goats, etorphine causes hypoxemia, pulmonary hypertension, hypoventilation, and hypercapnia.[13] The latter observations suggest that etorphine might be the cause of the various perturbations observed

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during capture of white rhinoceros. The pulmonary vascular effects of etorphine in white rhinoceros have yet to be investigated either in combination with other drugs, as described above, or in isolation.

In-depth systematic evaluation of the pulmonary effects of capture in general, and etorphine in particular, in white rhinoceros will require measurement of pulmonary vascular pressures and cardiac output (CO). In turn, these measurements will require catheterization of the pulmonary artery. Conventionally, in smaller species, pulmonary artery catheters are introduced percutaneously via a jugular vein. Preliminary investigations using ultrasound imaging suggested that tissue depth over the jugular vein renders this percutaneous route impractical even in young white rhinoceros; however, those investigations suggested the linguofacial vein as a likely alternative access route.

To refine a technique for pulmonary artery catheterization, the authors had the opportunity to perform a pilot study on five boma-habituated white rhinoceros. This allowed them to assess a pulmonary artery catheter design and to attempt to measure pulmonary artery pressure (PAP) and CO for the first time in rhinoceros. The white rhinoceros were immobilized with etorphine plus azaperone, followed by butorphanol. Once instrumentation was complete and a set of measurements had been collected, a supplemental dose of etorphine was given intravenously. This supplementation mimics the conditions that might pertain if an increment of etorphine were to be given to prolong immobilization in the field, and it allowed changes in PAP and CO after supplemental etorphine to be observed. In the horse, which is closely related phylogenetically to rhinoceros, sympathetic tone increases after etorphine administration; hence mean PAP and CO were expected to increase with supplemental etorphine in the rhinoceros.[1,15]

MATERIALS AND METHODS

This study was approved by the University of Pretoria Animal Ethics Committee (project number V101-15) and the South African National Parks Animal Use and Care Committee (reference number 001/16).

Five white rhinoceros (one adult female, two subadult females, one subadult male, and one male calf), weighing between 1,012 and 1,514 kg, were captured in Kruger National Park (23°49′60″S, 31°30′90″E; altitude 317 m), South Africa, and habituated to captivity for at least 6 mo. The rhinoceros were housed individually in rhinoceros-specific holding pens (bomas) and were given ad libitum water and a mixture of lucerne (*Medicago sativa*) and tef (*Eragrostis tef*) hay. Feces were removed from the enclosures, water troughs cleaned, and food replaced daily. The health of the rhinoceros was evaluated daily by trained personnel using a scoring system based on feed intake; volume, consistency, and color of feces; and behavior.[14]

Rhinoceros were darted in the holding pens with a combination of etorphine (Elanco, Kempton Park 1619, South Africa; 9.8 mg/ml) and azaperone (Janssen Pharmaceuticals Ltd., Halfway House 1685, South Africa; 40 mg/ml). Drugs were administered intramuscularly in the nuchal hump or rump using a 3.0-ml plastic dart with a 60-mm uncollared needle fired from a compressed air rifle (DAN-INJECT International S.A., Skukuza 1350, South Africa). Doses were selected on the basis of previously measured body mass and were 1.98 μg/kg (minimum, maximum 1.86, 2.26 μg/kg) of etorphine and 0.019 mg/kg (0.015, 0.026 mg/kg) of azaperone. Once a rhinoceros could be safely approached, it was blindfolded and positioned in either right ($n = 3$) or left ($n = 2$) lateral recumbency. Butorphanol (5 mg for every 1 mg of etorphine, or 0.01 mg/kg; Wildlife Pharmaceuticals, White River 1240, South Africa) was administered intravenously as soon as the animal was positioned in lateral recumbency.

After aseptic skin preparation, a 22 standard wire gauge 2.5-cm over-the-needle intravenous catheter (Nipro Medical Corporation, Bridgewater, NJ 08807, USA) was inserted into an auricular artery. Mean systemic arterial blood pressure (ABP) was measured using a transducer (TranStar 60-inch single monitoring kit, Ref MX950T, Smiths Medical ASD, Inc., Dublin, OH 43017, USA) connected to a physiologic monitor (Cardiocap/5 Datex-Ohmeda, GE Healthcare, Helsinki 00510, Finland). When the transducer was plugged into this monitor, the monitor automatically performed a static calibration at 100 mm Hg. The transducer was zeroed at the level of the manubrium sterni before the beginning of data collection for each rhinoceros and then again just before administering supplemental etorphine. Both transducer and monitor give results that are accurate (within ±2 mm Hg) between 0 and 300 mm Hg (technical reference manuals for the above transducer and monitor); this was confirmed post hoc for the range of pressures measured using a mercury manometer. Arterial blood was also sampled anaerobically

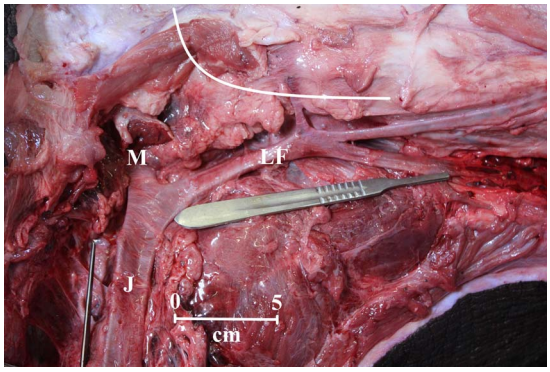

Figure 1. Dissection of the right linguofacial vein, ventrolateral view, in a white rhinoceros calf killed by poachers. Overlying skin, subcutis, muscle, and glandular tissue have been removed. Rostrad is to the right. The curved white line represents the angle of the mandible. J, jugular vein; M, maxillary vein; LF, linguofacial vein.

from the catheter for immediate analysis of blood gas tensions using the VetScan® i-STAT 1® handheld analyzer and precalibrated CG8+ cartridges (Abbott Point of Care Inc., Princeton, NJ 08540, USA). Values for blood gas tensions were corrected to pulmonary artery temperature. Heart rate was determined by auscultation of the thorax.

The linguofacial branch of the jugular vein was located ventro-medial to the angle of the mandible (Fig. 1) using ultrasonography (Hitachi Noblus® ultrasound system fitted with a C25 convex 5–1 MHz transducer, Hitachi Aloka Medical Ltd, Wallingford, CT 06492, USA). Following standard aseptic skin preparation, a keyhole incision was made through the skin overlying the vein. Using ultrasonographic guidance, a 6 or 8 cm-long 12-ga needle (Intraflon 2, Vygon, 95440-Ecouen, France) was inserted through the incision and into the vein. Once venous blood was observed in the needle hub, a wire guide was inserted through it. With the wire guide in situ, the needle was removed, and a dilator and 11 Fr percutaneous sheath introducer (Super Arrow-Flex Sheath Set®, Teleflex Medical, Morrisville, NC 27560, USA) were inserted over the wire guide into the vein. After removal of the dilator, a sterile, custom-built, 160-cm 8 Fr Swan-Ganz-type thermodilution pulmonary artery catheter (Gaeltec Devices Ltd., Dunvegan, Isle of Skye, United Kingdom IV55 8GU) was inserted through the introducer and down the jugular vein. Pressure in the catheter was measured using a transducer (TranStar 60-inch single monitoring kit, ref. MX950T) connected to another physiologic monitor (Advisor Vital Signs Monitor, Smiths Medica). As with the monitor used to measure systemic ABP, when the transducer was plugged into this monitor, it also automatically performed a static calibration at 100 mm Hg. The transducer was zeroed at the level of the manubrium sterni before the beginning of data collection for each rhinoceros and then again just before administering supplemental etorphine. This transducer and physiologic monitor also give results that are accurate (within ±2 mm Hg) between 0 and 300 mm Hg (technical reference manuals for the above transducer and monitor). This was also confirmed post hoc for the range of pressures measured using a mercury manometer. The tip of the catheter was passed through the right heart and into the pulmonary artery while observing the characteristic pressure waveforms on the monitor. The ability of the catheter to wedge in a branch of the pulmonary artery was assessed by inflating and deflating the balloon on the catheter while observing the pressure waveform.

CO was measured by thermodilution (PM-9000 Vet veterinary portable multiparameter patient monitor, ShenZhen Mindray Bio-Medical Electronics Co., Ltd., Nanshan, ShenZhen, China). The thermistor in the pulmonary artery catheter had the same properties as the thermistor used in Arrow balloon thermodilution catheters (Arrow International Inc., Reading, PA 19610, USA). The appropriate computation constant for that thermistor (0.308) and an injectate volume of 6 ml were entered into the multiparameter patient monitor. Sixty milliliters of ice-cold 0.9% saline was injected by hand as rapidly as possible (<3 sec) through the side port of the introducer in the linguofacial vein. The same individual gave all injections of indicator (RDG). After multiplying by a factor of 10, the median of three to five sequential measurements was calculated and recorded; no values were discarded. Supplemental etorphine 0.30 (0.23, 0.36) μg/kg was given intravenously 61 min (53, 76 min) after the initial injection of etorphine and azaperone. Pulmonary and systemic pressures, CO, heart rate, and arterial blood gases were measured within the 20 min before supplemental etorphine was given intravenously and again within the 10 min after it was given.

The rhinoceros were prepared for recovery after the last data collection point by removing all monitoring devices, removing the arterial catheter and linguofacial vein introducer, applying pressure until adequate hemostasis had been

achieved, administering an antibiotic (florfenicol, Nuflor®, Merck & Co./Merck Sharp & Dohme Corp., Halfway House 1685, South Africa) and nonsteroidal anti-inflammatory drug (meloxicam, Metacam®, Boehringer Ingelheim, Randburg, 2125 South Africa), and clearing the boma of people. At this time, 0.11 mg/kg (0.09, 0.14 mg/kg) of naltrexone (Kyron Laboratories, Benrose 2094, South Africa) was administered intravenously to antagonize the etorphine.

A priori, mean PAP and CO were selected as the variables of primary interest. Commercial software was used for data analysis (GraphPad Prism® 7 for Windows, version 7.03, 2017, GraphPad Software, Inc., La Jolla, CA 92037 USA). Because of the small sample size, values were assumed to be nonnormally distributed; hence the nonparametric Wilcoxon signed-rank test, one-tailed, was used to test the significance of differences between pre- and postetorphine values. Differences between pre- and postetorphine heart rate, mean systemic ABP, arterial partial pressure of oxygen (PaO_2), and arterial partial pressure of carbon dioxide ($PaCO_2$) were also tested using the Wilcoxon signed-rank test. Data are presented as median (minimum, maximum).

RESULTS

Time to lateral recumbency after darting was 9 min (8, 11 min). The pulmonary artery was accessed in all five rhinoceros with this catheter. However, the catheter could not be wedged in the pulmonary arterial bed of any of them. Pulmonary arterial temperature of the rhinoceros before supplemental etorphine was 37.4°C (35.8, 37.8°C), and 37.7°C (36.2, 38.2°C) after supplemental etorphine. Ambient temperature was 22.4°C (17.7, 28.1°C) at the start of data collection.

Mean PAP was 35 mm Hg (32, 47 mm Hg) and increased 83% (28, 106%) ($P = 0.031$) to 64 mm Hg (60, 68 mm Hg) after the bolus of etorphine (Fig. 2A). Cardiac output was 120 L/min (92, 145 L/min) and increased 27% (3, 43%) ($P = 0.031$) to 150 L/min (119, 171 L/min) after the bolus of etorphine (Fig. 2B). Heart rate increased by 20% (4, 45%) ($P = 0.031$, Fig. 2C); mean systemic ABP increased in four rhinoceros and decreased in one ($P = 0.09$, Fig. 2D). PaO_2 decreased by 47% (20, 72%) ($P = 0.031$, Fig. 2E), whereas $PaCO_2$ increased in four rhinoceros and decreased in one ($P = 0.06$, Fig. 2F).

Time from darting to standing after immobilization was 79 min (67, 92 min). All rhinoceros were immobilized and recovered uneventfully.

DISCUSSION

These experiments confirm that pulmonary artery catheterization and thermodilution CO measurement are feasible in anesthetized white rhinoceros. They also show that in rhinoceros of this size, the pulmonary artery catheter needs to be longer than 160 cm to wedge in a branch of the pulmonary artery if the linguofacial vein is used for vascular access. Wedging is necessary to measure pulmonary arterial occlusion pressure (PAOP).

Mean PAP was ~35 mm Hg before the supplemental dose of etorphine was given (Fig. 2A). Normal values for PAP are not available for white rhinoceros; however, these values are similar to those reported in standing horses.[8,9,17] The location of the tip of the pulmonary artery catheter might have been several centimeters above or below the reference level (manubrium sterni), leading to an unmeasured hydrostatic offset to the values for mean PAP. A method for correcting for this has been described but, unfortunately, the method requires continuous pressure recording that was not available for these experiments.[17] Nevertheless, the pulmonary artery catheter tip was not manipulated during pressure observations; hence the changes in pressure observed after etorphine (Fig. 2A) are immune from this offset.

After a relatively small, supplemental dose of etorphine, mean PAP increased ~83% and CO increased ~27%. The increase in PAP with etorphine is qualitatively consistent with observations in goats, whereas CO decreased after etorphine in goats rather than increasing as it did in the white rhinoceros.[13] Normal values for CO are not available for white rhinoceros. However, applying allometric scaling principles to the body masses of these animals predicts that their normal CO would be 55 L/min (51, 70 L/min).[16] Allometric scaling predicts that normal heart rate in these animals would be 42 beats/min (39, 43 beats/min); this is similar to heart rates measured in unmedicated, standing white rhinoceros.[5,16] Before supplemental etorphine, the values for both CO and heart rate that were measured were more than two times greater than their allometric correlates. The increase in CO, heart rate, and apparent increase in systemic ABP that was observed after supplemental etorphine in rhinoceros (Fig. 2B, C, D) agrees qualitatively with those caused by etorphine in horses; an increase in PAP was also observed in the white rhinoceros after supplemental etorphine; however, to the authors' knowledge, there are no data available

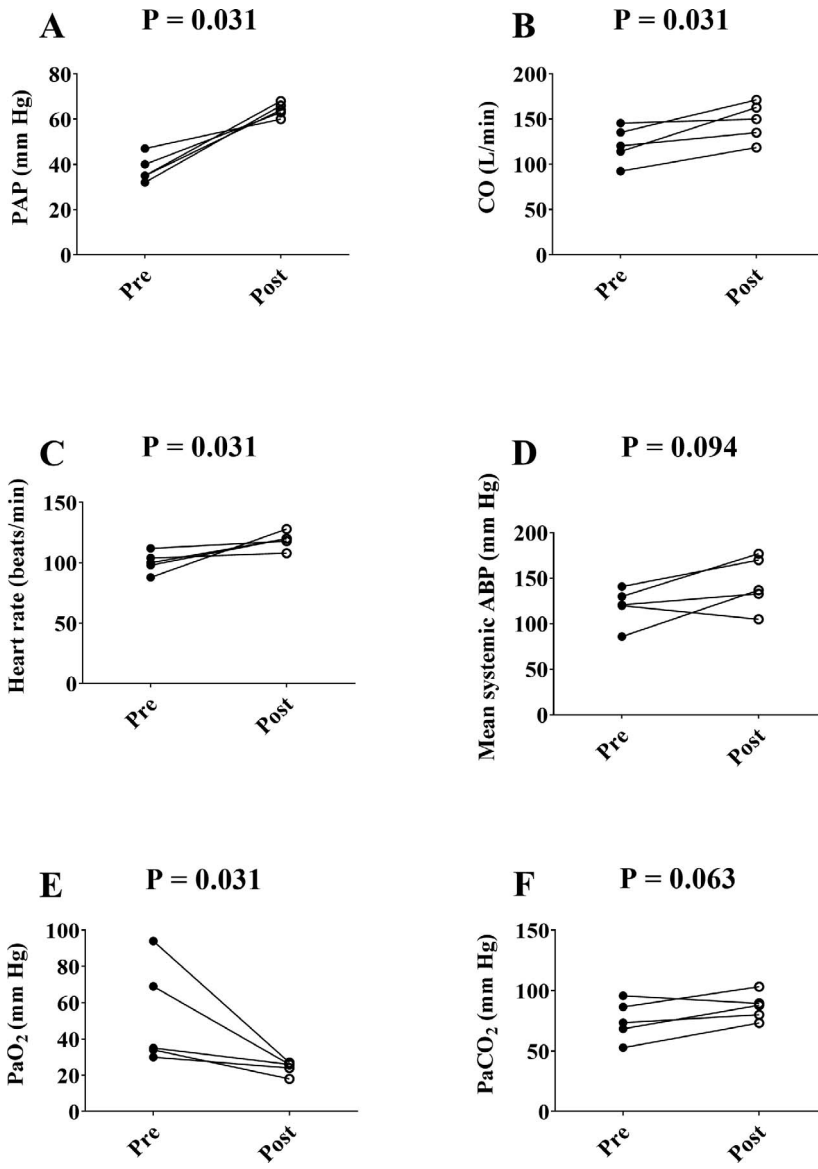

Figure 2. (**A**) Mean pulmonary artery pressure (PAP), (**B**) cardiac output (CO), (**C**) heart rate, (**D**) mean systemic arterial blood pressure (ABP), (**E**) arterial partial pressure of oxygen (PaO_2), and (**F**) arterial partial pressure of carbon dioxide ($PaCO_2$) in five white rhinoceros before and after supplemental etorphine, 0.25–0.5 mg given intravenously. "Pre" indicates measurements (closed circles) taken before supplemental etorphine; "post" refers to those taken after supplemental etorphine (open circles).

for PAP in horses after etorphine.[6,12,15] In the horse, it has been postulated that the increase in CO, heart rate, and systemic ABP are the consequence of upregulated sympathetic nervous activity with etorphine; this is supported by studies in horses that demonstrate increased plasma norepinephrine concentrations after etorphine administration, and mitigation of tachycardia and systemic arterial hypertension by preemptive β-adrenoceptor blockade.[1,6] In white rhinoceros immobilized with etorphine and azaperone, plasma epinephrine concentration correlates positively and negatively, respectively, with tremor intensity and PaO_2, lending indirect support to a thesis that sympathetic upregulation might be responsible for the increases in PAP, CO, and heart rate reported here after etorphine.[7] Most of the rhinoceros were hypoxemic and all

were hypercapnic before supplemental etorphine, and the supplemental etorphine appeared to exacerbate the hypoxemia and hypercapnia. Because hypoxemia and hypercapnia likely upregulate sympathetic activity, these data do not allow distinction between a possible direct effect of etorphine on sympathetic tone and an indirect effect mediated by inhibition of pulmonary gas exchange.

All Stewart–Hamilton indicator dilution methods for CO, such as the thermodilution method used here, assume that the indicator is conserved.[19] The transit time of the indicator—ice-cold saline—between the injection site in the linguofacial vein and the thermistor in the pulmonary artery was longer than it would have been had the injection been made into the right atrium or the jugular vein, as is usual in smaller species; this almost certainly caused loss of thermal indicator (by cooling of perivascular tissue) and, thus, systematic overestimation of true CO. These data do not allow estimation of the magnitude of this discrepancy in these rhinoceros. However, because the method for measuring CO remained the same, it is assumed that this offset applies equally to measurements before and after supplemental etorphine, and that it does not contribute to the change detected after supplemental etorphine.

The increase in PAP that was observed could be due to increased blood flow or resistance in the arterial segment of the pulmonary bed, increased left ventricular preload, increased left ventricular afterload, or some other cause. In addition to the measurements of PAP and CO that have been shown to be feasible in white rhinoceros, analysis of the mechanisms behind the increase in PAP will require, at least, measurement of PAOP (which is a surrogate for left atrial pressure) and calculation of pulmonary vascular resistance. Experiments where $PaCO_2$ and PaO_2 are maintained in a normal range will be necessary to investigate whether hypoxemia and hypercapnia are necessary intermediates in the cardiovascular effects of etorphine.

Before supplemental etorphine, four of five rhinoceros were hypoxemic ($PaO_2 < 80$ mm Hg, Fig. 2E), and all five were hypercapnic ($PaCO_2 > 40$ mm Hg, Fig. 2F); this is compatible with considerable pulmonary impairment caused by the initial capture drugs and subsequent recumbency. Since these animals did not run during the darting process, the hypoxemia and hypercapnia were probably caused by pulmonary depression from the drugs given during the initial chemical restraint. The decrease in PaO_2 and increase in $PaCO_2$ observed after supplemental etorphine (Fig. 2E, F) are compatible with additional functional impairment of gas exchange and decreased alveolar ventilation from the etorphine, although the possibility that these changes were part of ongoing processes initiated by the initial immobilization cannot be excluded. The increase in PAP with etorphine should increase capillary hydrostatic pressure and thus increase the rate of transit of water from the pulmonary capillaries to the interstitium of the lung.[19] If the lymphatic system cannot accommodate this increased load, water will accumulate in the lung.[19] This might impede pulmonary gas diffusion and hence contribute to the decrease in PaO_2 observed after etorphine. Equilibration of hemoglobin in erythrocytes with the alveolar gas takes a finite time; the increase in CO observed with etorphine might decrease the transit time of erythrocytes in the lung sufficiently to prevent such equilibration and thus contribute to the hypoxemia. Other perturbations of the pulmonary system might also contribute to the hypoxemia associated with etorphine in white rhinoceros.

The limited number of subjects available made this study underpowered for formally assessing the statistical significance of changes in multiple variables. Also, without suitable control experiments where etorphine was not given, it is possible that the changes observed after supplemental etorphine might have occurred anyway. In any case, the observations on the effects of supplemental etorphine reported here are inevitably biased by the etorphine, azaperone, and butorphanol given during initial immobilization ~1 hr previously. Nevertheless, the temporal relationship of the profound changes that were observed to the time that supplemental etorphine was given allows postulation of a causal relationship with some confidence. The use of supplemental etorphine seemed to be associated with serious adverse cardiopulmonary effects; this argues against the use of etorphine to prolong immobilization in white rhinoceros and suggests that alternative drugs are preferable, e.g. tranquilizers, sedatives, or dissociative agents.

CONCLUSION

These preliminary data suggest that etorphine has profound effects on the cardiopulmonary system of white rhinoceros that could compromise them during chemical immobilization. Further studies are required to confirm the effects of etorphine when it is given alone, and to dissect the

mechanisms responsible for these effects on the cardiopulmonary system and their possible relationship to hypoxemia. Such studies will inform efforts to ameliorate the adverse effects of etorphine or the search for viable alternatives to etorphine.

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