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BUTORPHANOL AND AZAPERONE AS A SAFE ALTERNATIVE FOR REPEATED CHEMICAL RESTRAINT IN CAPTIVE WHITE RHINOCEROS (*CERATOTHERIUM SIMUM*)

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Abstract: Anesthesia in the white rhinoceros (*Ceratotherium simum*) has routinely involved potent narcotic anesthetic agents such as etorphine or carfentanil with their associated adverse side effects. In captive rhinoceroses conditioned to routine handling, a combination of butorphanol and azaperone at mean (± SD) doses of 69.3 ± 18.0 mg and 103.1 ± 20.9 mg, respectively, was used to produce levels of neuroleptanalgesia ranging from light ''standing'' sedation to deeper planes of anesthesia producing sternal and lateral recumbency. This combination was used for repeated (minimum repeat frequency of 3 days between events) anesthetic episodes (n = 26) in two animals, with the remaining episode performed in a white rhinoceros with chronic renal disease. The action of butorphanol was satisfactorily reversed with naltrexone (125 mg i.v. and 125 mg i.m.). Results (mean ± SD) include sternal recumbency achieved in 14.1 ± 8.1 min after i.m. dosing, standing and ambulation occurred in 1.7 ± 0.6 min after reversal, heart rate was 62.0 ± 10.1 beats/min, respiratory rate was 14.7 ± 5.6 breaths/min, and percentage of oxygen saturation of hemoglobin (Spo_2) was 89.2 ± 3.0%. Without supplementation, the total elapsed time ranged from 44.9 min to 103.0 min, whereas elapsed times up to 214.3 min were achieved with supplementation (mean time to supplementation was 28.0 ± 13.9 min after initial dosing). Butorphanol and azaperone produced adequate muscle relaxation and apparently adequate analgesia for minor surgical interferences, including abdominal laparoscopy. Respiratory rates and Spo_2 measurements were improved compared with reports of using more potent opioids in this species.

Key words: Butorphanol, azaperone, rhinoceros, narcotics, chemical restraint, anesthesia.

INTRODUCTION

Anesthesia in the African rhinoceros species has routinely involved use of potent narcotic anesthetic agents and their associated adverse side effects, with hypoxia being one of the most significant and potentially life-threatening complications.[5,7,14,17] A mixture of butorphanol and detomidine has been used in the rhinoceros, but this combination produced undesirable side effects at dosages needed for recumbency.[11] A combination of butorphanol and azaperone has been used in this study of captive rhinoceros to produce standing and recumbent restraint for procedures such as foot work and abdominal laparoscopy.[15] In this report, we detail the use of butorphanol and azaperone for chemical restraint in three white rhinoceros (*Ceratotherium simum*) and compare the parameters of heart rate, respiratory rate, and percentage of oxygen saturation of hemoglobin (Spo_2) with other published narcotic protocols in the white rhinoceros.

CASE REPORT

Multiple anesthetic events (n = 27) were performed with a combination of butorphanol (Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA; 10 mg/ml) and azaperone (Stresnil, Janssen Pharmaceutica, Mississauga, Ontario L5N 5R9, Canada; 40 mg/ml) in three captive southern white rhinoceros (estimated body weight of 2,250 kg). One male was immobilized once weekly for 10 wk and then biweekly for 20 wk for treatment of a hoof wall defect. The other male was immobilized on one occasion to allow evaluation of chronic renal failure. The female was immobilized five times to facilitate diagnosis of a chronic right uterine horn enlargement. Two of the anesthetic events in this female were performed on a single day to allow placement of a cervical implant followed by later evaluation; the initial procedure was reversed successfully with 10 mg naloxone (Narcan, DuPont Pharmaceuticals, Manati, Puerto Rico 00701; 1 mg/ml) given intravenously (i.v.) and did not preclude repeat narcotic anesthesia 6 hr later.

Butorphanol and azaperone were mixed together in a syringe immediately prior to use and delivered intramuscularly (i.m.) by hand injection in the neck region with an 18-gauge, 38 mm (1.5-inch) needle, except for one occasion when the mixture was given i.v. All rhinos were immobilized with a mean (± SD) intramuscular dose of 69.3 ± 18.0 mg butorphanol tartrate and 103.1 ± 20.9 mg azaperone. A blindfold was applied once the rhinoceros was head-pressing or recumbent. At the conclusion of each procedure, the butorphanol was antagonized

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with 125 mg naltrexone i.v. and 125 mg i.m (Trexonil, Wildlife Pharmaceuticals, Fort Collins, Colorado 80524, USA; 50 mg/ml).

The monitoring protocol included cardiothoracic auscultation, monitoring of heart and respiratory rates, and pulse oximetry. Heart rates obtained during auscultation and oximeter-recorded pulse rates were compared to ensure accuracy. Continuous real-time pulse rate and Spo_2 readings were obtained during all but the first anesthetic event with a portable pulse oximeter (Nellcor N-20PA, Vet-Sat large sensor, Nellcor Inc., Hayward, California 94545, USA) from the dependent ear or, occasionally, a skin fold near the anus.

Data are presented as the observed range and the mean ± SD. Anesthetic dosage levels are summarized in Table 1, with an average of the means also reported in the results for serial measurements (pulse rate, respiratory rate, and Spo_2). Times were measured from hand injection of anesthetic drug combination. The first observed signs of drug effects usually consisted of disorientation, lowering of the head, or mild ataxia. Total elapsed time was the time from hand injection of the anesthetic combination to a return to standing (if recumbent) or normal ambulation after standing restraint. Complete recovery occurred from all anesthetic episodes.

Initial drug administration always produced sternal recumbency in both males. Supplemental dosing with butorphanol was necessary for 12 of 27 (44%) anesthetic events, with a mean (± SD) dose of 28.7 ± 9.8 mg given i.v. or i.m. (Table 2). Once settled in sternal recumbency, the rhinos were always pushed into lateral recumbency on rubber pads in order to facilitate medical procedures. In contrast, the female rhinoceros remained standing and head-pressing except for occasional short periods of recumbency that usually followed supplemental dosing of butorphanol by intravenous bolus. On one occasion, ''standing'' anesthesia was maintained with an intravenous constant rate infusion of butorphanol at a rate that varied from 0.6 mg to 1.8 mg/min (100 mg butorphanol added to 1 L 0.9% NaCl delivered i.v. at 1–3 drops/sec via a 10 drop/ml intravenous set).

After intramuscular dosing, the time to first effect ranged from 1.1 min to 6.8 min (mean ± SD = 3.8 ± 1.1 min). Intramuscular dosing in the males produced sternal recumbency in a period ranging from 5.6 min to 25.2 min (mean ± SD = 12.4 ± 6.0 min). All anesthetic events were reversed without complication, and recumbent animals were standing in 1.0–3.6 min (mean ± SD = 1.7 ± 0.6 min). Mild sedation for several hours and

Table 1. Accumulated data from anesthesia in three captive southern white rhinoceros (*Ceratotherium simum*) with a combination of butorphanol and azaperone.

Animal name	Number of events	Butorphanol (mg)	Azaperone (mg)	Time to first effect (min)	Time to-sternal recumbency (min)	Dose of naltrexone (mg; 50% i.v., 50% i.m.)	Time to standing postreversal (min)	Total elapsed time (min)	Mean respiratory rate (breaths/min)	Mean Spo_2 (% O_2 saturation of hemoglobin)	Mean heart rate (beats/min)
	1	50[a]	40[a]	1.1	65.0	250	1.0	103	31	n/c[b]	76
	5	50	100	4.2	17.5	250	1.6	83.4	16.8	90	52.6
Mtondo	15	70	100	3.8	9.8	250	1.8	64.5	13.9	88.9	59.7
Mac	1	100	120	3.1	25.2	250	2.2	91.4	11	82	62
	1	50	100	6.8	35.5	250	1.7	156.0	11	95	60
	1	100	160	4.1	27.7	250	1.0	125.1	14	89	85
	1	50[a]		3.1	n/a	naloxone 10[a]	n/a[c]	90.0	n/c	89	74
	1	100	100	4.5	n/a	250	n/a	87.3	11	91	82
Pokey	1	120	160	1.5	n/a	250	n/a	214.3	12	89	75

[a] Intravenous administration.
[b] n/c = data not collected.
[c] n/a = not applicable.

Table 2. Summary of supplemental dosages used to maintain anesthesia after induction with butorphanol and azaperone in the white rhinoceros (*Ceratotherium simum*).

Animal name	Events requiring supplementation at each dose	Induction dosage		Mean supplemental dosage			
				Supplemental butorphanol		Supplemental azaperone	
		Butorphanol (mg)	Azaperone (mg)	Dose (mg)	Time[a] (min)	Dose (mg)	Time[a] (min)
Mtondo	0 of 1	50[b]	40[b]				
	3 of 5	50	100	25[b]	23.9	40	25.1
	5 of 15	70	100	28.4[b]	26.3	60	46.1
Mac	1 of 1	100	120	50[b]	23.8	40[b]	23.8
Pokey	1 of 1	50	100	30	17.1	40	25.4
	1 of 1	100	160	40[b]	23.1	40	32.0
	0 of 1	50[b]					
	0 of 1	100	100				
	1 of 1	120	160	0.6–1.8 mg/min CRI[c]	69.1	50	130.8

[a] Time between primary drug administration and first supplemental dose.
[b] Intravenous administration; all other doses given i.m.
[c] Intravenous constant rate infusion (CRI) of butorphanol.

occasional ataxia were noted after reversal with naltrexone, presumably secondary to residual azaperone effects. Without supplementation, the total elapsed time ranged from 44.9 min to 103.0 min, whereas elapsed times up to 214.3 min were achieved with supplementation (mean time to supplementation was 28.0 ± 13.9 min after initial dosing).

Averaging the data for the 27 anesthetic events, the mean pulse rate ranged from 43 to 85 beats/min (mean ± SD = 62.0 ± 10.1 beats/min), and the mean respiratory rate ranged from 9 to 31 breaths/min (mean ± SD 14.7 ± 5.6 breaths/min). The mean Spo_2 readings ranged from 82 to 95% (mean ± SD = 89.2 ± 3.0%), whereas assessment of each anesthetic event individually revealed an Spo_2 range from 55 to 97%.

DISCUSSION

Potent opioid analgesics generally serve as the cornerstone of rhinoceros immobilization and anesthesia in both the wild and captivity. However, one of the most notorious adverse effects of these drugs is hypoxia secondary to direct depression of central nervous system respiratory centers, diminished response to elevated arterial carbon dioxide, and alveolar collapse.[7,8,12,14,20] A protocol involving prophylactic and symptomatic treatment of opioid-induced respiratory depression with doxapram HCl and nalorphine is commonly used in field immobilizations.[7,14]

Butorphanol, a synthetic opioid agonist-antagonist, has fewer respiratory depressant effects than most pure opioid agonists due in part to weak antagonism at the mu receptor and a predilection for kappa-receptor activation.[1,2] In addition, the respiratory depression of agonist-antagonists reaches a ''ceiling'' beyond which supplemental or higher doses do not cause further depression.[1] Azaperone, a butyrophenone derivative, is marketed for use in pigs and is also used in a wide variety of wild animals.[3,10,13,19] In the rhinoceros, its primary use has been in the field situation in combination with etorphine.[4,14,16,19] Butyrophenones have minimal effects on respiration and have been shown to actually increase ventilation in pigs, horses, and humans.[1,17] It has also been proposed to inhibit some of the respiratory depressant actions of both opioids and general anesthetics.[4,8,13,19]

Respiratory rates as low as 2–6 breaths/min have been reported with the use of etorphine in the white rhinoceros.[5,14] Spo_2 readings under etorphine anesthesia in this species are generally between 80 and 85%, with reports below 50% in some cases.[7,14,17] With the butorphanol/azaperone combination in the white rhinoceros reported here, respiratory rates averaged 15 breaths/min with mean Spo_2 values ranging from 86 to 95%. One short episode of poor Spo_2 readings (range 55–69% over 5 min) was noted in one anesthesia during initial recumbency, but other vital parameters were within normal limits. Use of butorphanol and detomidine in the rhinoceros has been reported, although dosages sufficient to produce recumbency resulted in hypoxemia that required treatment with nasal oxygen.[11]

The level of analgesia provided by the butorpha-

nol in this combination was considered sufficient for invasive medical procedures, including aggressive treatment of severe hoof problems and standing laparoscopic surgery. Although a local block was used to provide additional analgesia at the sites of laparoscopic trocharization, adequate visceral analgesia was present to allow extensive manipulation of abdominal organs, CO_2 insufflation of the peritoneal cavity, and uterine biopsy.[15] Assessment of analgesic quality was based on minimal changes in heart and respiratory rates and lack of arousal. The combination was used to provide sedation and analgesia for up to 3.5 hr. Such a procedure would not likely have been feasible with the use of etorphine or carfentanil because of the severe respiratory compromise expected from both the resulting recumbency and the depressant effects of the drug. Antagonism of the opioid component of this combination with naltrexone provided rapid return to standing/ambulation with minimal residual effects; the occasional mild ataxia and sedation observed after reversal were likely secondary to azaperone and were considered insignificant.

The butorphanol/azaperone mixture was administered i.v. for induction of anesthesia in one male on one occasion. He developed mild excitement characterized by elevation of the head to a ''star-gazing'' position, marked ataxia, and eventual relaxation into a ''dog-sitting'' position. This effect was considered undesirable. Intravenous butorphanol has been reported to produce CNS excitement in the horse and other species[6,9,12,20]; however, no adverse effects were noted with intravenous use in a juvenile southern black rhino ($n = 12$)[16] or in one white rhino (''Pokey''; Table 1). Intravenous administration of azaperone to horses is occasionally followed by a period of bizarre reactions such as various degrees of excitement and ataxia and relaxation in the rear quarters with splayed forelimbs.[3,13,18] Therefore, it is possible that the unexpected reactions seen in this rhino were more a product of the intravenous azaperone than of the butorphanol, and thus intramuscular administration of azaperone is recommended.

The use of butorphanol and azaperone for chemical restraint in captive rhinoceros that are accustomed to human presence and contact can allow routine veterinary work to be performed while eliminating the need for more potent opioids. Furthermore, butorphanol and azaperone are less hazardous to handle because of their lower potency. Thus, the butorphanol/azaperone combination provides a safe alternative to potent opioids by avoiding undesirable side effects in the anesthetized animal and by reducing the risks related to human narcotic exposure.

CONCLUSIONS

1) The combination of butorphanol and azaperone may be used intramuscularly to produce safe anesthesia in the captive white rhinoceros.

2) It may be used for repeated anesthetic episodes in the same animal.

3) It produces adequate muscle relaxation and apparently adequate analgesia for minor surgical interferences. Local anesthetic drugs may be used to supplement the analgesia.

4) It produces less respiratory depression and hypoxia than alternative techniques that use potent mu agonist opioids on the basis of comparisons of respiratory rate and Spo_2 with prior published reports of narcotic anesthesia in this species.

5) Its action can be satisfactorily reversed with naltrexone.

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LITERATURE CITED

1. Bailey, P. L., and T. H. Stanely. 1994. Narcotic intravenous anesthetics. *In:* Miller, R. D. (ed.). Anesthesia. Churchill Livingston, New York, New York. Pp. 281–366.

2. Bowdle, T. A. 1988. Clinical pharmacology of antagonists of narcotic-induced respiratory depression: a brief review. Acute Care. 12(Suppl. 1): 70–76.

3. Dodman, N. H., and A. E. Waterman. 1979. Paradoxical excitement following the intravenous administration of azaperone in the horse. Equine Vet. J. 11: 33–35.

4. Haigh, J. C. 1990. Opioids in zoological medicine. J. Zoo Wildl. Med. 21: 391–413.

5. Heard, K. J., J. H. Olsen, and J. Stover. 1992. Cardiopulmonary changes associated with chemical immobilization and recumbency in a white rhinoceros (*Ceratotherium simum*). J. Zoo Wildl. Med. 23: 197–200.

6. Kamerling, S., T. Wood, D. DeQuick, T. J. Weckman, C. Tai, J. W. Blake, and T. Tobin. 1989. Narcotic analgesics, their detection and pain measurement in the horse: a review. Equine Vet. J. 21: 4–12.

7. Kock, M. D., P. Morkel, M. Atkinson, and C. M. Foggin. 1995. Chemical immobilization of free-ranging white rhinoceros (*Ceratotherium simum simum*) in Hwan-

ge and Matobo National Parks, Zimbabwe, using combinations of etorphine (M99), fentanyl, xylazine, and detomidine. J. Zoo Wildl. Med. 26: 207–219.

8. Kreeger, T. J. 1997. Handbook of Wildlife Chemical Immobilization. International Veterinary Services, Inc., Laramie, Wyoming.

9. LeBlanc, P. H. 1991. Chemical restraint for surgery in the standing horse. Vet. Clin. North Am. Equine Pract. 7: 521–532.

10. Marsboom, R. 1969. On the pharmacology of azaperone, a neuroleptic used for restraint of wild animals. Proc. Int. Symp. Wild Anim. Med. Vet. Res., Antwerp, Belgium. 1968: 155–161.

11. Morris, P. 1996. *In:* Fouraker, M., and T. Wagener (eds.). AZA Rhinoceros Husbandry Resource Manual. Cockrell Printing Co., Fort Worth Zoological Park, Fort Worth, Texas. Pp. 46–49.

12. Muir, W. W., and J. A. Hubbell. 1991. Equine Anesthesia: Monitoring and Emergency Therapy. Mosby Year-Book, St. Louis, Missouri.

13. Plumb, D. C. 1999. Veterinary Drug Handbook, 3rd ed. Iowa State Univ. Press, Ames, Iowa.

14. Raath, J. P. 1994. Anaesthesia of the white rhino. *In:* Penzhorn, B. L., and N. P. J. Kriek (eds.). Proc. Symp. Rhinos Game Ranch Anim, Onderstepoort, Republic of South Africa. 1994: 119–127.

15. Radcliffe, R. M., D. A. Hendrickson, G. L. Richardson, J. R. Zuba, and R. W. Radcliffe. 2000. Standing laparoscopic-guided uterine biopsy in a southern white rhinoceros (*Ceratotherium simum simum*). J. Zoo Wildl. Med. 31: 201–207.

16. Radcliffe, R. W., D. E. Paglia, and C. G. Couto. 2000. Acute lymphoblastic leukemia in a juvenile southern black rhinoceros (*Diceros bicornis minor*). J. Zoo Wildl. Med. 31; 71–76.

17. Rogers, P. S. 1993. Chemical capture of the white rhinoceros (*Ceratotherium simum*). *In:* McKenzie, A. A. (ed.). The Capture and Care Manual. The South African Veterinary Association, Pretoria, Republic of South Africa. Pp. 119–127.

18. Serrano, L., and P. Lees. 1976. The applied pharmacology of azaperone in ponies. Res. Vet. Sci. 20: 316–323.

19. Swan, G. E. 1993. Drugs used for the immobilization, capture and translocation of wild animals. *In:* McKenzie, A. A. (ed.). The Capture and Care Manual. The South African Veterinary Association, Pretoria, Republic of South Africa. Pp. 2–59.

20. Thurmon, J. C., W. J. Tranquilli, and G. J. Benson (eds.). 1996. Lumb & Jones' Veterinary Anesthesia, 3rd ed. Williams and Wilkins, Baltimore, Maryland.

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