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CARDIORESPIRATORY EFFECTS OF MEDETOMIDINE BUTORPHANOL, MEDETOMIDINE–BUTORPHANOL–DIAZEPAM, AND MEDETOMIDINE–BUTORPHANOL–KETAMINE IN CAPTIVE RED WOLVES (CANIS RUFUS)

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Abstract: Safe, effective, and reversible immobilization protocols are essential for the management of free-ranging red wolves (*Canis rufus*). Combinations using an α_2-adrenoceptor agonist and ketamine have been shown to be effective for immobilization but are not reversible and can produce severe hypertension and prolonged or rough recoveries. To minimize hypertension and provide reversibility, 24 red wolves were immobilized using three medetomidine–butorphanol (MB) combinations without the use of ketamine in the initial injection. All wolves were administered medetomidine (0.04 mg/kg i.m.) and butorphanol (0.4 mg/kg i.m.). Seven wolves received no other immobilization agents (MB wolves), nine received diazepam (0.2 mg/kg i.v.) at the time they were instrumented (MBD wolves), and eight received ketamine (1 mg/kg i.v.) 30 min after instrumentation (MBK30 wolves). Physiologic parameters were monitored during immobilization. The heart rate was similar among the three groups for the first 30 min, and marked bradycardia was noted in one wolf from each group. Hypertension was observed initially in all three groups but was resolved within 10–30 min. The MBK30 wolves had significant elevations in heart rate and transient hypertension after intravenous ketamine administration. Most wolves had mild to moderate metabolic acidemia. Immobilizing drugs were antagonized in all wolves with atipamezole (0.2 mg/kg i.m.) and naloxone (0.02 mg/kg i.m.). The medetomidine-butorphanol-diazepam wolves were also given flumazenil (0.04 mg/kg i.v.). All wolves were standing within 12 min and were fully recovered within 17 min. Medetomamine-butorphanol and MBD combinations provided effective and reversible immobilization of red wolves without the sustained hypertension associated with the use of α_2-adrenoceptor agonist–ketamine combinations. Delaying the administration of ketamine reduced its hypertensive effects.

Key words: *Canis rufus*, red wolf, medetomidine, butorphanol, immobilization, diazepam, ketamine, atipamezole, naloxone, flumazenil.

INTRODUCTION

The red wolf (*Canis rufus*) is a critically endangered species that was extirpated from the southeastern United States during the 20th century.[14] A captive propagation and reintroduction program has been undertaken to restore red wolves to a portion of their former range.[14] Intensive management techniques are necessary to monitor and maintain the health of this free-ranging population. Consequently, many red wolves are immobilized on several occasions during their lifetime, and some may be immobilized many times in a year. A safe, effective, and rapidly reversible immobilization protocol is essential for these procedures because many of these animals are returned immediately to the wild.

For several years the United States Fish and Wildlife Service (USFWS) has used a xylazine–ketamine combination for immobilizing captive and free-ranging red wolves. But rough and prolonged recoveries have been a concern with the use of this combination. Medetomidine is an α_2-adrenoceptor agonist that is more potent and more highly α_2-receptor–selective than is xylazine.[19] It has been used extensively for the immobilization of captive and free-ranging carnivores[5] because it is rapidly and completely antagonized by administration of atipamezole, a specific α_2-adrenoceptor antagonist.[18] In 1998 an investigation was conducted with captive red wolves to evaluate the cardiorespiratory effects of xylazine–ketamine, medetomidine–ketamine, medetomidine–ketamine–acepromazine, and medetomidine–ketamine–butorphanol.[17] Marked hypertension was documented with each of the four drug combinations. In humans, acute hypertensive events of similar severity have caused cerebral infarction, acute pulmonary edema, hypertensive encephalop-

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athy, and acute congestive heart failure.[20] Pulsus alterans, a sign of imminent left ventricular failure, has been observed in dogs with acute hypertension after the combined administration of medetomidine and atropine.[8]

The additive hypertensive effects of medetomidine and ketamine have been documented in domestic dogs.[6] But medetomidine–butorphanol combinations have been shown to induce profound, reversible sedation in domestic dogs.[1] The purpose of this investigation was to determine whether medetomidine–butorphanol would provide safe, effective, and reversible immobilization of red wolves while reducing acute hypertension. In this study the sedative and cardiorespiratory effects of medetomidine–butorphanol were evaluated in the same population of captive red wolves as previously reported.[17] Because of concerns that this combination may not provide immobilization of adequate depth or duration, medetomidine–butorphanol–diazepam and medetomidine–butorphanol with delayed supplementation of a low dosage of ketamine were also investigated.

MATERIALS AND METHODS

Twenty-four adult, captive red wolves (12 male and 12 female) were used in a between-subjects experimental design, between November 1999 and January 2000. The median age of wolves was 5 yr (range = 2–9 yr). Eight of the wolves were housed at the North Carolina Zoological Park (NCZP), and 16 were housed at the USFWS, Alligator River National Wildlife Refuge (ARNWR). The wolves were housed outdoors in groups of one to four, with access to den boxes. Average daily temperatures from November to January for these regions are 3–14°C (National Weather Service, http://www.nws.mbay.net/normtemp.html). The wolves at ARNWR were fed a commercial dry dog food diet (Hill's Pet Nutrition Inc., Topeka, Kansas 66601, USA) and had access to water ad libitum. The NCZP wolves were fed a commercial dry dog food diet (Purina Mills, Inc., St. Louis, Missouri 63144, USA) supplemented with Nebraska Canine Diet (Nebraska Brand, North Platte, Nebraska 69103, USA) and had access to water ad libitum.

Each wolf was randomly assigned to one of the three experimental groups—medetomidine-butorphanol (MB), medetomidine-butorphanol-diazepam (MBD), or medetomidine-butorphanol-ketamine (MBK30). All wolves received an initial intramuscular injection of medetomidine hydrochloride (Domitor, Pfizer Animal Health, Exton, Pennsylvania 19341, USA; 0.04 mg/kg i.m.) and butorphanol (Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA; 0.4 mg/kg). The MB wolves (n = 7) received no other immobilization agents, the MBD wolves (n = 9) received diazepam (Valium, Hoffman-La Roche, Nutley, New Jersey 07110, USA; 0.2 mg/kg i.v.) at the time of instrumentation (T = 0), and the MBK30 wolves (n = 8) received ketamine hydrochloride (Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA; 1 mg/kg) 30 min after instrumentation (T = 30).

The wolves were fasted for at least 24 hr before immobilization but were allowed access to water. The wolves were either hand-netted or confined to a den box or canine transport kennel before drug administration. Drug doses were based on estimates of body weight. Actual body weights were measured at the end of each procedure, and absolute dosages of immobilizing and reversal agents are reported on the basis of these weights. Medetomidine and butorphanol were combined in the same syringe and injected into the caudal hindlimb muscles. The wolves were left undisturbed for 15 min after injection (either the den box was closed or the wolves' eyes were covered with a towel).

Systolic, mean, and diastolic blood pressure were determined oscillometrically 15 min after injection with a cuff placed over the dorsal metatarsal artery (Dinamap, Critikon, Tampa, Florida 33614, USA). The cuff size (12–19 cm) was selected so that the width was 40% of the circumference of the limb. Wolves not fully immobilized at 15 min were left undisturbed for an additional 5 min. The wolves were then transported to a central processing area, where recording instruments were applied. Initial physiologic measurements (T = 0) were recorded within 3–5 min of the initial blood pressure measurements. Measurements were then recorded every 10 min for 50 min. Body temperature was measured using a digital thermometer inserted into the rectum. Heart rate and rhythm were monitored by electrocardiography (Vet/ECG 2000, Heska-SDI, Waukesha, Wisconsin 53186, USA). End-tidal CO_2 was measured using sidestream capnography (Vet/Cap Plus 7100, Heska-SDI, Waukesha, Wisconsin 53186, USA), with the sampling port near the rima glottis or within a naris. Respiratory rate was determined by observing chest excursions and by capnography. Indirect oxygen–hemoglobin saturation (SpO_2) was evaluated by pulse oximetry (Vet/Ox 4403, Heska-SDI, Waukesha, Wisconsin 53186, USA), with the probe attached to the tongue or lip. Blood gas determinations were done on samples taken anaerobically from the femoral artery at T = 0, 30, and 50 min. Arterial blood gas analysis (PaO_2, $PaCO_2$, pH) was performed using a portable

clinical analyzer (iSTAT with G3+ cartridge, Heska-SDI, Waukesha, Wisconsin 53186, USA). Blood gas values were corrected for body temperature using the equations developed for humans.[2] An intravenous catheter was placed in the cephalic vein.

Procedures performed included annual health examinations, venous blood collection, vaccination, dental prophylaxis, attachment of ear tags, and placement or removal of radio collars. At the end of the immobilizations (T = 50 min), the catheters were removed, the animals were transported to recovery areas, and antagonists were administered. Wolves at ARNWR recovered in their pens, whereas NCZP wolves recovered indoors in canine transport kennels. To minimize postreversal trauma, ARNWR wolves were gently restrained with a towel over their eyes for 5 min after injection of antagonists. All wolves received atipamezole hydrochloride (Antisedan, Pfizer Animal Health, Exton, Pennsylvania 19341, USA; 0.2 mg/kg i.m.) and naloxone (Naloxone HCl injection, Abbott Laboratories, North Chicago, Illinois 60064, USA; 0.02 mg/kg i.m.). Wolves in the MBD group also received flumazenil (Romazicon, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA; 0.04 mg/kg i.v.). Times from administration of antagonists to standing and to complete recovery were recorded.

Physiologic measurements were not obtained for all animals at all time points because of intentional early reversals (two MB wolves and one MBD wolf), one spontaneous reversal (MBD wolf), difficulties in obtaining arterial blood gas samples, and difficulties with monitoring equipment. Statistical analysis was performed using a Kruskall–Wallis test (SAS, SAS Institute, Cary, North Carolina 27513, USA) to determine differences between treatment group medians, at each time point, for all physiologic data. Values of $P < 0.05$ were considered statistically significant. Data are reported as median values with ranges. The effects of the fluid volumes administered were evaluated by determining correlation coefficients for each data set at each time point (SAS, SAS Institute).

RESULTS

The first signs of drug effect were observed within 5 min of medetomidine and butorphanol administration in all 24 wolves. The median (range) doses administered were medetomidine 0.039 (0.033–0.049) mg/kg and butorphanol 0.39 (0.33–0.49) mg/kg. Of the 24 wolves, 21 could be moved from their holding pens to the examination area within 15 min of drug administration. Two wolves required 20 min, and one wolf required 0.2 mg/kg i.v. diazepam, for adequate sedation. This latter wolf was included in the MBD group. Wolves in the MBD group received a median diazepam dose of 0.20 (0.19–0.24) mg/kg. Wolves in the MBK30 group received a median ketamine dose of 1.0 (0.92–1.05) mg/kg.

At the time of instrumentation (T = 0) all wolves were heavily sedated, were nonresponsive to external stimuli, and had good muscle relaxation. By T = 30, wolves in the MB and MBK30 groups were noticeably less sedate and had less muscle relaxation than did wolves in the MBD group. During the first 30 min, four of the seven MB wolves and six of the eight MBK30 wolves exhibited at least one of the following signs: muscle twitching, increased jaw tone, slight head movement in response to loud noises, ear manipulation, or dental scraping. These signs were eliminated after ketamine administration in all the MBK30 wolves. The MBD wolves were essentially nonresponsive to stimuli until T = 50, except for one wolf that recovered spontaneously at T = 25.

Median body temperatures were elevated (39.6–41.2°C; range = 37.6–42.2°C) in all three groups at T = 0. Eight wolves (four MB wolves, two MBD wolves, and two MBK30 wolves) had body temperatures exceeding 40°C. These wolves were treated with ambient-temperature intravenous fluids, isopropyl alcohol applied to the abdomen, footpads, and ears, and abdominal cold packs. Temperatures fell below 40°C within 30–40 min. Median temperatures of all wolves declined steadily over time and were not statistically different between groups at any time. Median body temperatures for all groups at T = 50 were 37.7–38.6°C (range = 36.4–40.4°C). Two wolves immobilized on an unusual day when ambient temperatures were <0°C developed body temperatures <36°C. These wolves were reversed after 20 and 40 min, respectively.

The volume of fluids administered did not differ significantly between the three groups (median = 5.8 ml/kg). Small volumes (1–8 ml/kg) of lactated Ringer's solution were administered to 11 wolves to maintain catheter patency. Hyperthermic animals (T > 40°C, $N = 9$) received larger volumes (11–26 ml/kg) of ambient-temperature fluids. There was a significant correlation between volume of fluids administered and body temperature at T = 0, T = 10, T = 20, and T = 30, but volume of fluids did not show a statistically significant correlation to any other physiologic parameter.

Heart rates were similar between all groups from T = 0 to T = 30 and until T = 50 for the MB and MBD groups. Median heart rates (Table 1) decreased over time in the MB and MBD groups. Two MB wolves and one MBD wolf had heart rates be-

Table 1. Median (range) values for heart rate and respiratory rate in immobilized red wolves.[a]

Time	MB	*n*	MBD	*n*	MBK30	*n*
			Heart rate (beats/minute)			
0	76 (40–102)	7	66 (42–114)	7	77 (44–108)	8
10	60 (40–79)	6	56 (45–96)	8	76 (40–86)	8
20	63 (38–80)	6	57 (49–84)	7	64 (48–82)	8
30	57 (32–64)	5	60 (48–70)	6	72 (46–80)	7
40	50 (38–82)	5	59 (36–84)	6	80* (52–108)	8
50	56 (34–85)	5	59 (36–80)	6	88* (52–94)	7
			Respiratory rate (breaths/minute)			
0	25 (14–30)	5	16 (12–24)	7	20 (14–52)	8
10	26 (12–30)	5	17 (12–24)	8	16 (12–36)	7
20	21 (12–26)	5	14 (10–17)	6	18 (14–24)	8
30	12 (10–24)	5	16 (12–20)	6	17 (14–22)	8
40	19 (16–20)	3	16 (12–20)	6	18 (16–24)	8
50	22 (14–24)	3	16 (12–20)	6	16 (12–22)	7

[a] MB, medetomidine–butorphanol; MBD, medetomidine–butorphanol–diazepam; MBK30, medetomidine–butorphanol–ketamine.
* Values for MBK30 are significantly different ($P < 0.05$) from those of MB and MBD.

low 40 beats per minute at T = 20, T = 30, and T = 40, respectively. Median heart rate increased in the MBK30 group after ketamine administration and differed significantly from both the MB group and the MBD group at T = 40 and T = 50. Transient periods (5–10 min) of second-degree heart block were seen in one MB wolf, two MBD wolves, and one MBK30 wolf. Persistent second-degree heart block was observed in two MBD wolves.

Respiratory rates were similar between the three groups at all time points. Median values ranged from 12–26 breaths per minute (Table 1). One MB wolf and one MBK wolf were panting at the beginning of the procedure, and the MB wolf continued to pant until reversal agents were administered.

Systolic, mean, and diastolic arterial blood pressure values were elevated when first measured but decreased over time in all three groups (Table 2). No statistically significant differences in blood-pressure measurements were detected between groups at any individual time point, but the lowest (54 mm Hg) and the highest (170 mm Hg) mean arterial pressures (MAPs) were observed in MBD wolves. Two MBD wolves experienced transient hypotension (MAP < 60 mm Hg)[12] at T = 10 and T = 30, respectively. Although 12 of the 24 wolves were considered hypertensive (diastolic arterial pressure > 116 mm Hg)[15] when blood pressure was first measured, only 2 of the 24 were hypertensive at T = 30. Blood pressure increased in MBK30 wolves after ketamine administration, with four of the eight wolves experiencing hypertension, but the median increase was not statistically significant.

No significant differences in PaO_2, SpO_2, $PaCO_2$, end-tidal CO_2, arterial blood pH, or bicarbonate were detected between groups at any time point. Median PaO_2 values were ≥70 mm Hg throughout the procedure. But at T = 0, nine wolves (three MB, two MBD, and four MBK30) had PaO_2 values between 60 and 70 mm Hg, and one wolf (MB) had a PaO_2 value of 51 mm Hg. PaO_2 values were >70 mm Hg for these 10 animals at subsequent time points. Median SpO_2 was ≥93% (range = 84–99%) at all time points for all groups. Median $PaCO_2$ values for all groups were 33–43 mm Hg (range = 25–50 mm Hg). Median end-tidal CO_2 values for all groups were 30–45 mm Hg (range = 15–57 mm Hg). Median arterial blood pH values were 7.26–7.34 (range = 7.15–7.35). One wolf in each of the MB and MBD groups had a pH value below 7.20 at T = 0, but pH increased above 7.20 for both these animals by T = 30. Median bicarbonate values were 16–20 mM/L (range = 13–24 mM/L).

For reversal, all wolves received a median dose (range) of 0.19 (0.17–0.24) mg/kg atipamezole and 0.019 (0.017–0.024) mg/kg naloxone. MBD wolves received a median dose of 0.041 (0.038–0.049) mg/kg flumazenil. Of the 24 wolves, 21 recovered fully within 10 min after administration of the reversal agents. The three remaining wolves (one from each group) were standing within 12 min and were fully recovered at 17 min. Median time to standing and median time to recovery did not differ among groups. Median time to standing for all groups was 6 min, and median time to full recovery was 7 min. MB and MBD wolves did not show postimmobil-

Table 2. Median (range) values for arterial blood pressure in immobilized red wolves.[a]

Time	MB	*n*	MBD	*n*	MBK30	*n*
			Systolic arterial pressure (mmHg)			
Initial	166 (124–182)	7	150 (98–194)	7	129 (90–188)	7
10	148 (114–172)	6	166 (82–201)	8	156 (114–176)	7
20	150 (88–162)	6	160 (88–183)	7	142 (127–168)	7
30	146 (61–162)	5	143 (80–172)	6	143 (128–166)	8
40	141 (117–150)	4	143 (96–162)	6	158 (140–162)	8
50	138 (123–152)	5	135 (116–178)	6	160 (138–165)	7
			Mean arterial pressure (mmHg)			
Initial	140 (94–156)	7	136 (74–170)	7	116 (66–158)	7
10	132 (78–142)	6	137 (54–149)	8	118 (94–148)	7
20	122 (76–130)	6	128 (76–140)	7	112 (92–146)	7
30	122 (61–128)	5	118 (58–151)	6	122 (112–131)	8
40	114 (83–128)	4	130 (70–142)	6	129 (105–148)	8
50	106 (96–126)	5	118 (106–146)	6	124 (106–142)	7
			Diastolic arterial pressure (mmHg)			
Initial	124 (74–140)	7	124 (56–161)	7	144 (52–144)	7
10	114 (60–120)	6	120 (48–132)	8	112 (76–132)	7
20	106 (58–114)	6	114 (60–122)	7	100 (82–130)	7
30	104 (39–114)	5	107 (42–138)	6	108 (98–115)	8
40	101 (64–112)	4	94 (64–122)	6	118 (92–130)	8
50	97 (86–116)	5	105 (78–132)	6	110 (78–128)	7

[a] MB, medetomidine–butorphanol; MBD, medetomidine–butorphanol–diazepam; MBK30, medetomidine–butorphanol–ketamine.

ization drug effects, whereas MBK30 wolves exhibited mild ataxia for 5–10 min after recovery. Only one spontaneous recovery (one MBD wolf at T = 25) occurred before the end of the 50-min procedure. One MBD wolf was found dead in its den 5 days after being immobilized. At postmortem examination this animal was found to have a gastric dilatation and volvulus with signs of endotoxemia.

DISCUSSION

The results of this investigation demonstrate that the combined effects of medetomidine and butorphanol provide a level of sedation and analgesia that is adequate to perform many of the field techniques required for red wolf population management. Procedures such as physical examinations, vaccination, blood collection, dental prophylaxis, attachment of ear tags, and placement of radio collars could readily be performed. The sedative effects of the MB combination lasted 30–50 min, and the addition of either diazepam or ketamine prolonged the immobilization time and provided a deeper plane of sedation.

Moderate to severe hyperthermia (T > 40°C)[13] was evident in several of the wolves and was consistent with other reports describing immobilization of red and gray wolves.[4,17] High body temperatures may have been caused by muscular exertion, physical restraint, stress, or drug interference with thermoregulatory mechanisms.[13] Hyperthermia resolved after treatment with intravenous fluids, isopropyl alcohol, and cold packs. Initial hyperthermia is common in excited animals that must be pursued for immobilization. It is important that mechanisms for cooling animals be available when performing immobilization procedures because hyperthermia can cause marked hypotension, shock, severe cardiac arrhythmias, and death.[13]

Fluid administration was considerably variable among the subjects, raising the possibility that physiologic parameters might have been affected. Administration of fluids can lower heart rate, increase blood pressure, and improve tissue perfusion.[16] Increased tissue perfusion may in turn alleviate metabolic acidosis, facilitating oxygen delivery and carbon dioxide transport. In this study the volume of fluids administered did not have a statistically significant correlation with any physiologic parameter except for body temperature, so we do not believe that fluids significantly affected the results.

Median heart rates of MB and MBD wolves were lower than those previously reported for red wolves immobilized with medetomidine–ketamine or xylazine–ketamine,[17] although at most time points they were within the range reported for healthy,

awake dogs (56–180 beats/min).[19] Heart rates were highest in wolves receiving ketamine. Profound bradycardia is commonly observed in domestic dogs that receive α_2-adrenoreceptor agonists,[7] as a result of a compensatory parasympathetic reflex to peripheral vasoconstriction.[11] Such bradycardia occurs independent of centrally mediated sedation and analgesia and is best left untreated unless accompanied by hypotension. Although several wolves in this study were bradycardic, they did not have concurrent hypotension. MAP remained above 60 mm Hg in all but two MBD wolves that experienced transient hypotension. Second-degree heart block was detected in six of the wolves in this study, but this condition is considered a common, benign, parasympathetic reaction to α_2-adrenoreceptor agonists.[7]

Hypertension appears to be a common finding in immobilized wild canids.[10,17] In the domestic dog, hypertension has been defined as an indirect systolic arterial pressure greater than 202 mm Hg, an indirect diastolic pressure greater than 116 mm Hg, or both.[15] Normal resting blood pressure values are not available for red wolves. But reports of median blood pressure values in habituated gray wolves (*Canis lupus*) suggest that they are similar to domestic dogs,[10] so similar cutoff values for hypertension would seem appropriate. Transient hypertension was observed in immobilized wolves in this study. Only 2 of the 24 wolves (8%) were considered hypertensive at T = 30, in contrast to a previous study in which 23 out of 32 red wolves (72%) immobilized with α_2-adrenoreceptor agonist–ketamine combinations had diastolic pressures that exceeded 116 mm Hg at T = 30.[17] The transient hypertension we observed was likely because of a combination of elevated catecholamine levels and transient drug effects. Without the sympathoadrenal effects of ketamine, blood pressure decreased below hypertensive levels over time. The MBK30 wolves experienced only a transient elevation in blood pressure after ketamine administration, demonstrating that, as in domestic dogs,[3] delaying the administration of ketamine results in less severe hypertension in wolves that have received α_2-adrenoreceptor agonists.

Wolves in each of the three groups maintained adequate ventilation and oxygenation. Respiratory rates were within normal limits and were similar to those previously reported for immobilized red wolves, gray wolves, and domestic dogs.[4,9,17] Arterial $PaCO_2$ and end-tidal CO_2 values were consistent with each other and indicated adequate minute ventilation. One wolf experienced transient hypoxemia, suggesting that a source of 100% oxygen should be available when using these drug combinations. Median SpO_2 values for MB wolves were higher than the mean values reported for the use of medetomidine–butorphanol–ketamine (MBK) in red wolves.[17] This indicates that, in addition to having beneficial cardiovascular effects, MB also causes less respiratory depression than does the MBK combination.

Mild to moderate metabolic acidemia (low median bicarbonate values with median $PaCO_2$ within normal limits) was observed in all but one wolf. Metabolic acidosis occurs commonly with immobilization of wildlife, particularly with excitement, physical exertion, and associated anaerobic metabolism. These factors likely contributed to the mild to moderate acidosis observed. The transient hypoxemia documented in some wolves may also have contributed to anaerobic metabolism and acidosis.

All three combinations were reliably reversible. Such reversibility may be invaluable for working with free-ranging red wolves because it will facilitate safe and rapid release of immobilized animals. Wolves in the MBK30 group exhibited slight ataxia for up to 5 min after reversal, probably due to the residual effects of the low dosage of ketamine. Wolves immobilized with this combination may need to be held for an additional 10–15 min before release.

In conclusion, all three protocols provided effective immobilization. But our results suggest that the MB combination offers several advantages for routine field use (procedures lasting 20–30 min). These two drugs, which can be mixed in the same syringe and administered intramuscularly, are fast acting, cause relatively mild adverse cardiorespiratory effects, and can be completely reversed at any time during a procedure. For longer procedures, either the MBD or the MBK30 combination can be used. MBD induces more profound sedation, but the diazepam must be given intravenously. The water-soluble benzodiazepine, midazolam, could be used in place of diazepam, and mixed with medetomidine and butorphanol in the same syringe, but both benzodiazepines require the additional expense of flumazenil reversal. The MBK30 combination is useful for longer procedures but may cause some unwanted cardiovascular effects. As ketamine is not reversible, rough recoveries are expected if the other agents are antagonized within 30 min after ketamine administration.

Further studies will be necessary to identify specific applications of the MB, MBD, and MBK30 regimens. By reducing the risk of severe hypertension and improving the quality of recovery, the use of these combinations should have benefits for the

management of red wolves and other free-ranging canids.

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LITERATURE CITED

1. Bartram, D. H., M. J. Diamond, A. S. Tute, C. W. Trafford, and R. S. Jones. 1994. Use of medetomidine and butorphanol for sedation in dogs. J. Small Anim. Pract. 35: 495–498.

2. Gem®Premier Plus. 1996. Gem®Premier Plus Reference Manual. Instrumentation Laboratory, Lexington, Massachusetts.

3. Haskins, S. C., J. D. Patz, and T. B. Farver. 1986. Xylazine and xylazine–ketamine in dogs. Am. J. Vet. Res. 47: 636–641.

4. Holz, P., R. M. Holz, and J. E. F. Barnett. 1994. Effects of atropine on medetomidine/ketamine immobilization in the gray wolf (*Canis lupus*). J. Zoo Wildl. Med. 25: 209–213.

5. Jalanka, H. H., and B. O. Roeken. 1990. The use of medetomidine, medetomidine–ketamine combinations, and atipamezole in nondomestic mammals: a review. J. Zoo Wildl. Med. 21: 259–282.

6. Jalanka, H., K. Skutnabb, and Y. Damsten. 1989. Preliminary results on the use of medetomidine–ketamine combinations in the dog. Acta Vet. Scand. 85: 125–127.

7. Ko, J. C. H., J. E. Bailey, L. S. Pablo, and T. G. Heaton-Jones. 1996. Comparison of sedative and cardiorespiratory effects of medetomidine and medetomidine–butorphanol combinations in dogs. Am. J. Vet. Res. 57: 535–540.

8. Ko, J. C., S. M. Fox, and R. E. Mandsager. 2001. Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs. J. Am. Vet. Med. Assoc. 218: 52–58.

9. Kreeger, T. J., M. Callahan, and M. Beckel. 1996. Use of medetomidine for chemical restraint of captive gray wolves (*Canis lupus*). J. Zoo Wildl. Med. 27: 507–512.

10. Kreeger, T. J., U. S. Seal, and A. M. Faggella. 1986. Xylazine hydrochloride–ketamine hydrochloride immobilization of wolves and its antagonism by tolazoline hydrochloride. J. Wildl. Dis. 22: 397–402.

11. MacDonald, E., B. K. Kobilka, and M. Scheinin. 1997. Gene-targeting: homing in on alpha$_2$-adrenoceptor-subtype function. Trends Pharmacol. Sci. 18: 211–219.

12. Muir, W. W., and D. Mason. 1996. Cardiovascular system. *In:* Thurmon, J. C., W. J. Tranquilli, and G. J. Benson (eds.). Lumb and Jones' Veterinary Anesthesia, 3rd ed. Williams and Wilkins, Baltimore, Maryland. Pp. 62–114.

13. Nielsen, L. 1996. Chemical immobilization of free-ranging terrestrial mammals. *In:* Thurmon, J. C., W. J. Tranquilli, and G. J. Benson (eds.). Lumb and Jones' Veterinary Anesthesia, 3rd ed. Williams and Wilkins, Baltimore, Maryland. Pp. 736–764.

14. Phillips, M. K., R. Smith, V. G. Henry, and C. Lucash. 1995. Red wolf reintroduction program. *In:* Carby, L. N., S. H. Fritts, and D. R. Seip (eds.). Ecology and Conservation of Wolves in a Changing World. Occasional Publication No. 35. Canadian Circumpolar Institute, Edmonton, Alberta, Canada. Pp. 157–168.

15. Remillard, R. L., J. N. Ross, and J. B. Eddy. 1991. Variance of indirect blood pressure measurements and prevalence of hypertension in clinically normal dogs. Am. J. Vet. Res. 52: 561–565.

16. Seeler, D. C. 1996. Fluid and electrolyte therapy. *In:* Thurmon, J. C., W. J. Tranquilli, and G. J. Benson (eds.). Lumb and Jones' Veterinary Anesthesia, 3rd ed. Williams and Wilkins, Baltimore, Maryland. Pp. 572–589.

17. Sladky, K. K., B. Kelly, M. R. Loomis, M. K. Stoskopf, and W. A. Horne. 2000. Cardiorespiratory effects of four α_2 agonist–ketamine combinations in captive red wolves. J. Am. Vet. Med. Assoc. 217: 1366–1371.

18. Vaha-Vahe, A. T. 1990. The clinical effectiveness of atimpaezole as a medetomidine antagonist in the dog. J. Vet. Pharmacol. Ther. 13: 189–205.

19. Virtanen, R., J. M. Savola, V. Sanno, and L. Nyman. 1988. Characterization of the selectivity, specificity and potency of medetomidine as an α_2-adrenoceptor agonist. Eur. J. Pharmacol. 150: 9–14.

20. Zampaglione, B., C. Pascale, M. Marchisio, and P. Cavallo-Perin. 1996. Hypertensive urgencies and emergencies: prevalence and clinical presentation. Hypertension 27: 144–147.

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