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REVERSIBLE IMMOBILIZATION OF FREE-RANGING POLAR BEARS WITH MEDETOMIDINE-ZOLAZEPAM-TILETAMINE AND ATIPAMEZOLE

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ABSTRACT: The objective of this study was to determine if the potent α_2 agonist, medetomidine, and its specific antagonist, atipamezole, could be effectively used to immobilize polar bears (*Ursus maritimus*). Specifically, our goal was to develop a drug combination containing medetomidine that addressed some of the problems such as prolonged recovery time, non-reversibility, and poor analgesia that have been identified with the currently preferred drug combination, zolazepam-tiletamine (Telazol® or Zoletil®). During 1995 and 1996, 51 free-ranging polar bears along the western coast of Hudson Bay, Canada, were immobilized with a combination of medetomidine, zolazepam, and tiletamine (MZT). Immobilization with MZT was characterized by a short induction time, low volume, reliable and predictable immobilization and reversibility, adequate analgesia, and relative safety in handling for field personnel. Few adverse physiological effects were observed in any target animals with the exception of a single bear which convulsed and died shortly after it was reversed from anesthesia with atipamezole. We conclude that MZT is an effective drug combination for immobilizing polar bears. However, because of an unexplained mortality, further investigation of the physiological effects of MZT and atipamezole is warranted.

Key words: Atipamezole, immobilization, medetomidine-zolazepam-tiletamine, polar bear, *Ursus maritimus*.

INTRODUCTION

Zolazepam and tiletamine, in a 1:1 combination by weight (Telazol® or Zoletil®), has been the preferred drug for immobilizing free-ranging polar bears (*Ursus maritimus*) over the past 10 yr (Stirling et al., 1989). When used in this species, the drug combination results in a relatively short induction time (e.g., generally <10 min), reliable and predictable immobilization, little adverse physiological effect, and safety in handling for personnel. However, there are some disadvantages to the combination which include lack of a known antagonist (to tiletamine), potential for lengthy recovery, and minimal analgesia at the dosages required for satisfactory immobilization (Haigh et al., 1985).

During 1995, we initiated a study to develop a new drug combination for immobilizing polar bears. Specifically, we wanted to determine whether drug combinations that included the potent α_2 agonist medetomidine could eliminate the shortcomings experienced with the combination of zolazepam and tiletamine. Medetomidine drug combinations have been shown to be effective immobilization agents in many non-domestic mammals, including captive polar bears (Jalanka and Roeken, 1990). As an adjunct to anesthesia, medetomidine significantly reduces the amount of other anesthetic agents required (Räihä et al., 1989), therefore, when used in free-ranging mammals, it could minimize the occurrence of prolonged recoveries. In addition, the potent sedative effect of medetomidine is rapidly and smoothly reversed by administering the α_2 antagonist, atipamezole (Jalanka and Roeken, 1990). Finally, medetomidine is a potent analgesic and this property is one of the features that provides its basis for clinical use (Vähä-Vahe, 1989). Herein, we present data which demonstrate that the combination of medetomidine-zolazepam-tiletamine (MZT) is effective for immobilizing polar bears, and that atipame-

zole can be used to reverse MZT immobilization.

MATERIALS AND METHODS

Between July 1995 and November 1996, we captured 51 polar bears along the west coast of Hudson Bay (57°00′ to 58°50′N and 92°25′ to 94°15′W), approximately 50 km east of Churchill, Manitoba, Canada. Bears were located from a helicopter and then immobilized by use of remote injection equipment (27 bears by Cap-Chur®, Palmer Equipment Co., Douglasville, Georgia, USA; and eight bears by Pax-Arms®, Telonics Inc., Mesa, Arizona, USA) (Stirling et al., 1989) or, in the case of cubs less than 1-yr-old, by pole syringe or hand injection. We initially estimated the mass of each bear to calculate the amount of drug it required, and subsequently determined its actual mass (to the nearest 0.5 kg) by an electronic load scale (Senstek, Saskatoon, Saskatchewan, Canada) linked between a sling, suspending the anesthetized bear, and a supporting aluminum tripod. Thus, we were able to determine the actual drug doses received by each bear. We recorded the time for, and behavior during, induction and recovery, as well as the reversal time after atipamezole was administered.

First physiological measurements were taken within 10 min after recumbency, and subsequent measurements were made at 20–30 min intervals throughout the period of immobilization. We recorded respiratory rate, tidal volume (Wright Respirometer, Ferraris Medical Limited, London, England), pulse rate, hemoglobin oxygen saturation (4402 Vet/Ox® pulse oximeter system, Sensor Devices Inc., Waukesha, Wisconsin, USA), and rectal temperature. Ambient temperatures during capture periods ranged between −30 C and 25 C. For ambient temperatures above 18 C, we erected a blind above the recumbent bear to minimize its exposure to direct sunlight and prevent its body temperature from increasing. However, in situations where the rectal temperature of a bear increased above 39 C, we administered cold water enemas to prevent hyperthermia. A vestigial premolar tooth was extracted from bears not previously captured and age, in years, was determined by sectioning and counting the cementum annuli (Stoneberg and Jonkel, 1966). We used an existing database to determine the age of animals that had been captured on previous occasions. At the conclusion of our measurements, we administered atipamezole (Antisedan®, Farmos Group, Turku, Finland) intravenously (i.v.) only, or i.v. and intramuscularly (i.m.) in equal volumes, at a dose that was three to four times the dose of medetomidine received to ensure that circulating medetomidine was fully antagonized and to avoid the occurrence of resedation (Jalanka and Roeken, 1990).

We prepared MZT solution at a 1:33 (by weight) ratio of medetomidine to zolazepam-tiletamine by adding 1 ml of medetomidine solution (6 mg/ml) to every 200 mg of lyophilized zolazepam-tiletamine (Telazol®, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa, USA; or Zoletil®, Laboratories Virbac B.P., Nice, France) such that 1 ml of MZT contained approximately 177.6 mg of active drug. The medetomidine solution was prepared by lyophilizing Domitor® (1 mg/ml; Farmos Group, Turku, Finland) and reconstituting it at a concentration of 6 mg/ml. Once in solution, we used MZT for up to 3 wk and noted no changes in the efficacy of the drug within this time period. We maintained MZT and atipamezole (5 mg/ml) solutions in a light-proof container under cool temperatures (10 C to 15 C).

RESULTS

We administered MZT to 24 female and 27 male polar bears ranging in age from 4 mo to 21 yr, and in body mass from 9 kg to 560 kg. Our intended dose of MZT for immobilization was 2.06 mg/kg (medetomidine at 60 μg/kg, and zolazepam and tiletamine at 1.0 mg/kg each). However, because we estimated body mass prior to immobilization and because nine bears required multiple injections (eight bears required two injections and one bear required three injections) for immobilization, the actual range of MZT doses we administered (Table 1) differed almost seven-fold between the minimum and maximum (1.17 to 7.66 mg/kg), and the range of atipamezole doses we administered differed nine-fold (95 to 846 μg/kg). Although these ranges are large, we did not observe any dose-related differences in the physiological or behavioral responses of the bears. We required only small volumes of MZT to immobilize most polar bears (Table 1) and, although nine polar bears required multiple injections of MZT for immobilization, the total volume administered never exceeded 10 ml.

We saw no evidence of adverse effects in 50 polar bears that received MZT and

TABLE 1. Immobilization features of medetomidine-zolazepam-tiletamine (MZT) combination and atipamezole in 51 free-ranging polar bears.

Feature	Mean	Median	Standard error	90th Percentile
Animals requiring a single injection for induction (n = 42)				
Medetomidine dose (μg/kg)	70	64	4	114
Zolazepam-tiletamine dose (mg/kg)	2.3	2.1	0.2	3.8
Induction time (min)	3.6	3.0	0.3	6.7
Induction volume (ml)	2.5	2.2	0.3	5.0
Animals requiring multiple injections for induction (n = 9)				
Medetomidine dose (μg/kg)	109	93	19	—
Zolazepam-tiletamine dose (mg/kg)	3.6	3.1	0.6	—
Induction time (min)	19.4	17	3.2	—
Induction volume (ml)	4.6	5	0.9	—
All animals (n = 51)				
Duration of anesthesia (min)	192.8	197.0	5.9	228
Atipamezole dose (μg/kg)	274	227	24	520
Recovery time (min)				
–atipamezole: i.v. only; n = 13	2.4	2.5	0.4	4.0
–atipamezole: ½ i.v. and ½ i.m.; n = 38	7.5	6.5	1.1	15.8

atipamezole. However, a single 1-yr-old female polar bear immobilized with MZT died shortly after it was reversed from anesthesia with atipamezole administered intravenously (dose = 383 μg/kg; atipamezole : medetomidine ratio = 2.5:1). Death followed marked hyperthermia (rectal temperature was 42.6 C, 25 min after reversal) and was probably a consequence of prolonged (approximately 8 min) and intense convulsions which commenced without premonitory signs 2 min after the bear was fully reversed. During the period of anesthesia, the polar bear displayed strong, stable physiologic function (based on heart and respiratory rates, and hemoglobin O_2 saturation). We administered cold water enemas to the anesthetized bear on two occasions as its rectal temperature remained relatively high (38.7 C to 40.3 C).

The induction period, defined as the time between when a bear was first administered MZT and when it became recumbent and safe to handle, was short (Table 1) and characterized by a predictable smooth sequence of behaviors. Polar bears exhibited only subtle ataxia and most often, simply stopped running, stood still for a time, then slowly sat back and gradually declined to a position of sternal recumbency. Immobilized bears exhibited relaxed head and limbs, no tongue withdrawal reflex or jaw tone, no palpebral reflex, and only occasional nystagmus. For purposes not addressed in this study, we maintained polar bears under anesthesia for approximately 3 hr (Table 1). During these periods, 23 bears required one additional dose of medetomidine (20–30 μg/kg i.v. or i.m.) at approximately 100 min following MZT administration, and six of these bears required a second equivalent dose at 175 min. The signs that prompted additional doses included increasing nystagmus, increasing reflex activity (palpebral and tongue withdrawal), and increasing jaw tone and movement, but did not include changes in physiological parameters, e.g. pulse and respiratory rate.

The pattern of recovery, after we administered atipamezole, was similarly predictable and uniform with the sequence of behaviors almost exactly the reverse of that of induction. Prior to reversal, all bears remained fully immobilized and were, therefore, administered atipamezole. The reversal time, which we defined as the time between administration of atipamezole and

when the bear was sitting or standing on four feet, was often within 10 min (Table 1). Recovery was more rapid in bears receiving atipamezole by i.v. route only. After reversal, bears were often well co-ordinated and none showed any evidence of aggressive behavior. We observed hind limb ataxia in a few recovered bears, but this gradually disappeared within 0.5 to 1 hr following reversal. We never observed resedation but, in most cases, our observations were limited to within 1 hr following reversal. Therefore, we were less likely to observe resedation if it occurred >1 hr after reversal.

To reduce variation between animals differing greatly in body size and physical maturity (e.g., 9 kg cub and 560 kg adult), we restricted our statistical analyses of physiological data to those measures taken from adult polar bears only (n = 34). As well, we pooled the physiological data from adult polar bears that did not receive additional doses of medetomidine following induction (n = 21) with the data from those that did (n = 13), as there were no statistical differences in physiological values between groups (Sokal and Rohlf, 1981: ANOVA for repeated measures, $P > 0.05$). Weight-specific minute volume and respiratory rate exhibited significant decreases within 120 min following MZT administration, but remained relatively constant afterward (Fig. 1). Pulse rate also appeared to decrease, but this trend was not statistically significant (F = 1.32, P = 0.277). Pulse and respiratory rates changed little during or in the five minute period following painful procedures such as tooth extraction or adipose tissue biopsy (for concurrent studies). Hemoglobin O_2 saturation increased significantly within 90 min following MZT administration, and remained constant afterwards. During the initial 90 min, 70% of our measures of hemoglobin O_2 saturation were ≥90% and all measures were ≥80%. After 90 min, 88% of our measures were ≥90% while the remaining measures were all >85%. For most polar bears, rectal temperature changed little throughout the period of anesthesia (Fig. 2). Of exception were five polar bears, captured during high ambient temperatures (>20 C), which required two to three cold water enemas each to maintain their rectal temperatures below 39 C.

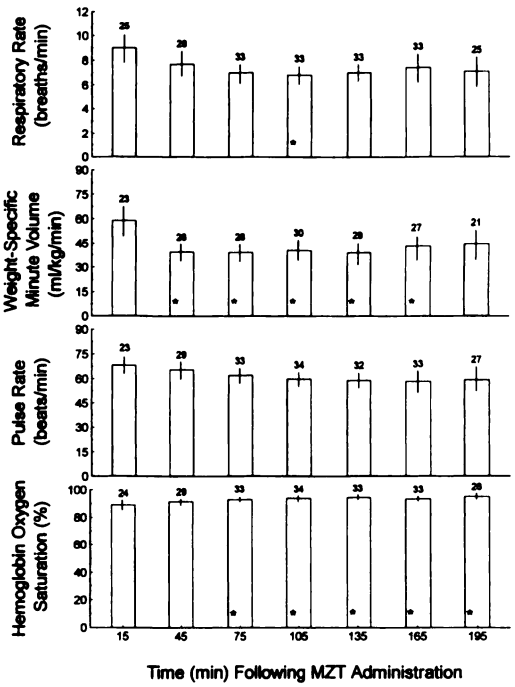

FIGURE 1. Changes in physiological measures (mean ± 95% confidence interval) of cardiopulmonary function in 34 free-ranging polar bears (>2 yr-of-age) following immobilization with MZT. The number above each bar represents the sample size at that time point. Asterisks (*) in bars indicate the value at that time point differed statistically ($P < 0.05$) from the value at 15 min (Sokal and Rohlf, 1981: ANOVA for repeated measures).

DISCUSSION

We conclude that MZT is an effective drug combination for immobilizing and anesthetizing polar bears based on a number of features. Firstly, we were able to safely administer MZT and atipamezole over a large range without observing any dose-related differences in the physiological or behavioral responses of the bears. However, we found MZT at 2.06 mg/kg (medetomidine at 60 μg/kg, and zolazepam and tiletamine at 1.0 mg/kg each) to

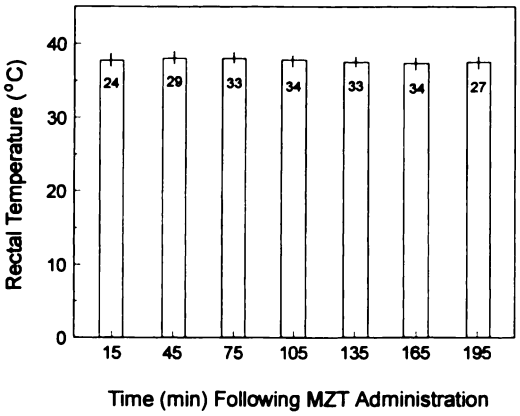

FIGURE 2. Changes in rectal temperature (mean ± 95% confidence interval) in 34 free-ranging polar bears (>2 yr-of-age) following immobilization with MZT. The number above each bar represents the sample size at that time point. Values at >15 min time points did not differ statistically ($P < 0.05$) from the value at 15 min (Sokal and Rohlf, 1981: ANOVA for repeated measures).

be an effective immobilizing dose for most bears. Secondly, we required only small volumes of MZT to immobilize most bears. Therefore, tissue damage was minimized at the site of injection, our darting accuracy was likely improved (as dart trajectories were more predictable), and we had increased opportunity to use low velocity darting systems, e.g., Pax-arm® darts. Nine bears required two or three injections before satisfactory immobilization. One possible explanation was that the darts we used in these instances may have been too short to penetrate into muscle and, consequently, much of the drug was delivered subcutaneously. Supporting this possibility is our observation that five of eight bears immobilized with Pax-arm® darts (dart length we used was ≤4.4 cm) required two injections. The other four animals requiring multiple injections were injected with longer Cap-chur® darts (dart length we used was ≥4.4 cm), but three of these bears were obese with large subcutaneous fat depots such that much of the MZT could have been injected subcutaneously. Thirdly, immobilization with MZT is characterized by good relaxation and analgesia which appears adequate (based on stable pulse and respiratory rates) for painful procedures most often employed, e.g., premolar extraction for aging. Finally, induction with MZT and reversal with atipamezole is reliable, predictable, and of short duration; thus, there is reduced likelihood of injury to the animal or field personnel. In addition, because we were able to safely administer atipamezole to polar bears by i.v. only and combined i.v. and i.m. routes, we were able to influence their duration of recovery. Therefore, if the general health of an anesthetized polar bear was being threatened, atipamezole could be administered i.v. for a rapid recovery.

In most anesthetized bears, we found cardiopulmonary function remained adequate and stable. There are few data published on normal ranges for physiological function in nonanesthetized polar bears. However, we observed respiratory rates in MZT-immobilized polar bears similar to those that we've observed in non-anesthetized, sleeping polar bears (unpublished data). The pulse rates of MZT-immobilized bears were similar to the range reported for nonanesthetized, sleeping polar bears of 40 to 65 beats/min (Øritsland, 1970). There are no data published for minute volume in polar bears. However, the minute volumes of mammals across a wide range of body masses can be predicted from established allometric equations (Stahl, 1967), and predicted mean values for minute volume range from 20.9 L/min for a 150 kg polar bear to 59.9 L/min for a 560 kg polar bear. Therefore, the range of weight-specific minute volumes (e.g. minute volume in ml/min ÷ body mass in kg) predicted for small to large adult polar bears is 139 to 107 ml/min/kg, respectively. This range is two to three times greater than the range of values we observed for polar bears immobilized with MZT (Fig. 1). This discrepancy between predicted and observed values could imply that respiratory function was markedly depressed in the anes-

thetized polar bears. This does not appear to be the case, however, as we observed hemoglobin oxygen saturation to remain >90%. If minute volume was seriously depressed, anesthetized bears should have developed hypoxia and hypercapnia (Guyton, 1986). The hypoxia, in turn, would have resulted in low hemoglobin oxygen saturation readings, e.g., <80%. The body temperatures of most anesthetized bears remained stable across a wide range of ambient temperatures, e.g. −30 C to 20 C. However, we recommend avoiding the immobilization of polar bears at temperatures >20 C as animals are at an increased risk for developing hyperthermia.

We are unable to explain why a single bear convulsed and died shortly after it was reversed from anesthesia with atipamezole. Specifically, we do not know what induced the convulsions and we have not seen any indication of convulsive behavior in other polar bears receiving MZT and atipamezole. In some species (e.g., dogs) recovering from Telazol® anesthesia, the tranquilizing effects of zolazepam appear to wane before those of tiletamine (Lin et al., 1992). Thus, muscle rigidity commonly occurs and some seizure-like activity may be observed, especially at higher doses (Short, 1989). Similarly, we have observed some rough recoveries characterized by mild clonic seizures in young (<2 yr) polar bears immobilized with Telazol® or Zoletil® alone. Rough recoveries might also be expected to occur in some young polar bears immobilized with MZT, after atipamezole has been administered and the sedative effect of medetomidine removed. However, if adverse responses to Telazol® are dose-related as in dogs, then rough recoveries should be fewer with MZT because of the lower dosage of zolazepam and tiletamine required.

Hyperthermia can also produce convulsions and death, if cerebral anoxia occurs (Fowler, 1995). We believe the bear which died was mildly hyperthermic based on rectal temperature recordings. If its body core temperature was significantly greater than its rectal temperature, e.g., >2 C, and if medetomidine can inhibit convulsive activity, then severe hyperthermia with cerebral anoxia may have occurred without our awareness. However, we have made simultaneous measures of rectal temperature and body core temperature (via a 40 cm rectal thermal probe) in six bears immobilized with MZT and found body core temperatures to be mildly increased (<1 C) from rectal temperatures (M. Cattet, unpubl. data). As well, two other bears immobilized with MZT had similar ranges of rectal temperatures (38.7 C to 40.1 C) and recovered uneventfully following reversal with atipamezole. A less probable explanation is that the convulsions were induced directly by the atipamezole. High doses of atipamezole administered i.v. in some animals can cause transient nervousness or overalertness (Jalanka and Roeken, 1990), but convulsions have not been described. Nonetheless, because the mortality remains unexplained, we believe further investigation of the physiological effects of MZT and atipamezole is warranted.

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