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ANESTHESIA OF POLAR BEARS USING XYLAZINE-ZOLAZEPAM-TILETAMINE OR ZOLAZEPAM-TILETAMINE

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ABSTRACT: Immobilization features and physiologic effects of combinations of xylazine-zolazepam-tiletamine (XZT) and zolazepam-tiletamine (ZT or Telazol®) were compared in nine captive and 17 free-ranging polar bears (*Ursus maritimus*) between 1998 and 2001. Although induction time was similar between drugs, induction dosage and volume were less with XZT. Induction of immobilization with XZT was predictable and smooth, muscle relaxation was good, and all bears remained completely immobilized and unresponsive to stimuli throughout a 1 hr handling period. The combination XZT was safely tolerated at two to three times the recommended dosage of 5 mg/kg (i.e., xylazine at 2 mg/kg + Telazol® at 3 mg/kg). Bears immobilized with XZT had slower pulse rates, higher mean arterial pressures, and lower arterial oxygen tensions than bears immobilized with ZT. Rectal temperature increased slowly over time (~0.5 C per hr) following immobilization with XZT. Based on response to a painful stimulus (compression of a claw bed), XZT was a more effective analgesic than ZT. Although the immobilization effects of XZT could not be reversed with the α_2 -antagonist drug tolazoline, they were reversed with yohimbine or atipamezole. However, the time to complete reversal of effects (i.e., standing and ambulatory) was highly variable among bears.

Key words: Anesthesia, atipamezole, polar bear, Telazol®, tiletamine, tolazoline, xylazine, yohimbine, zolazepam.

INTRODUCTION

A 1:1 mixture of zolazepam and tiletamine (Telazol®, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa, USA or Zoletil®, Virbac S.A., Carros, France) has long been recognized as the drug of choice for the chemical immobilization of bears (Stirling et al., 1989; Taylor et al., 1989; Gibeau and Paquet, 1991; White et al., 1996). Its advantages relative to other drug mixtures is that its anesthetic effects are highly predictable, it causes minimal depression of physiologic function, and it can be administered safely over a wide range of dosages (Cattet et al., 1999; Caulkett et al., 1999).

However, although generally effective and safe, the combination of zolazepam and tiletamine (ZT) does have some disadvantages (Cattet et al., 1999). For larger bears, ZT must be administered in relatively large volumes (≥ 7 ml), which can result in loss of accuracy with remote injection systems (dart rifles and darts) as well as increased tissue trauma at the site

of drug injection. The analgesic effect of ZT is poor and inadequate for painful procedures such as the extraction of a premolar for aging (Caulkett et al., 1999). The effects of ZT cannot be reversed because, although flumazenil may be used to reverse the effects of zolazepam, an antagonist drug for tiletamine does not exist. Finally, bears immobilized with ZT may have prolonged recoveries lasting many hours, especially if multiple doses are administered (Cattet et al., 1997).

Some limitations can be counteracted through the addition of an α_2 -agonist drug. Medetomidine has been mixed with ZT and used effectively to immobilize brown (*Ursus arctos*), polar (*U. maritimus*), and black bears (*U. americanus*) (Cattet et al., 1997; Caulkett and Cattet, 1997; Røken, 1997; Arnemo, 2001). The combination is administered at approximately 25% of the volume that would be required if using ZT alone. Further, medetomidine has potent analgesic effect and the combination of

medetomidine and ZT can be effectively and reliably reversed with the α_2 -antagonist atipamezole. Nevertheless, the widespread use of medetomidine in wildlife chemical immobilization is limited by its high cost and limited commercial availability in North America as a concentrated solution (>1 mg/ml).

In recent years, another α_2 -agonist drug, xylazine, has been used in combination with ZT to effectively and safely immobilize a variety of wildlife (Millspaugh et al., 1995; Sweitzer et al., 1997; Galka et al., 1999; Caulkett et al., 2000). In contrast to medetomidine, xylazine is relatively inexpensive, available widely, and has been used routinely for wildlife chemical immobilization. Here, data are presented from captive and free-ranging polar comparing the immobilization features and physiologic effects of combinations of xylazine-zolazepam-tiletamine (XZT) and zolazepam-tiletamine. Further, data are also presented regarding the effectiveness of the α_2 -antagonist drugs tolazoline, yohimbine, and atipamezole to reverse immobilization with XZT.

MATERIALS AND METHODS

Captive polar bears

Nine captive polar bears were immobilized with combinations of XZT or ZT at Churchill (Manitoba, Canada; 58°45'N, 94°06'W) in November 1998. These bears were considered problem animals and captured by government personnel with baited culvert traps or chemical immobilization (ZT, Telazol®, intramuscular at 6–8 mg/kg) and maintained in a holding facility for 3–23 days prior to this study. While held captive, each bear was immobilized on two occasions with 7 days between first and second immobilization. The protocols and type of data collected were identical for each immobilization event except that the drug combinations used differed between events with the sequence (i.e., ZT followed by XZT or vice versa) determined randomly.

Zolazepam-tiletamine was administered in a 1:1 combination by weight at an induction dose of 7–9 mg/kg based on estimated body weight. The drug was prepared as a solution (227 mg/ml) by adding 1.8 ml of sterile water for injection to 500 mg of lyophilized ZT resulting in a final volume of 2.2 ml per vial. The lyophilized

drug contributed approximately 0.4 ml to the final volume hence the greater volume of drug solution than added water. Xylazine-zolazepam-tiletamine was administered as xylazine (X, Xylamax®, MTC Pharmaceuticals Ltd., Cambridge, Ontario, Canada) and ZT in a 2:3 combination by weight at an induction dose of 5 mg/kg (i.e., 2 mg/kg X+3 mg/kg ZT). The drug was prepared as a solution (224 mg/ml) by adding 3.3 ml of X (100 mg/ml) to 500 mg of lyophilized ZT resulting in a final volume of 3.7 ml per vial. The lyophilized drug powder contributed approximately 0.4 ml to the final volume. Both combinations were delivered by pole syringe or blowpipe into the muscles of the shoulder or neck.

Within 15 min of immobilization the femoral artery was cannulated with a 20 ga×5 cm intra-arterial catheter (Surflo®, Terumo Medical Corp., Irvine, California, USA). The catheter was connected via non-compliant plastic tubing filled with heparinized saline to a pressure transducer (Uniflow®, Baxter Healthcare Corp., Irvine, California) that was, in turn, connected to a physiologic monitor (Propaq 400 EL, Protocol Systems Inc., Beaverton, Oregon, USA). The arterial line was used to measure pulse rate and direct arterial pressure and to remove arterial blood samples for blood gas analysis.

Pulse and respiratory rates and direct arterial pressures were recorded at 15 min following drug administration, and every 5 min afterwards until final measurements at 60 min following drug administration. Tidal volume (Wright's Respirometer, Haloscale, Penlon USA, Cleveland, Ohio, USA), percent hemoglobin saturation (SpO_2 ; 4402 Vet/Ox® pulse oximeter system, Sensor Devices, Waukesha, Wisconsin, USA), and rectal temperature (Excel 10® digital thermometer, AMG Medical, Montreal, Quebec, Canada) were recorded, and arterial blood samples (2–3 ml) were collected at 15, 30, 45, and 60 min following drug administration. For tidal volume measurement the respirometer was attached to a form-fitting facemask that was placed over the rostrum and mouth of the anesthetized bear. Blood samples were analyzed immediately after collection using a portable analyzer and blood gas cartridges (I-STAT Portable Clinical Analyzer and I-STAT G3+ Blood Gas Cartridges, I-STAT Corporation, East Windsor, New Jersey, USA). At 60 min, blood was collected from the jugular vein into sterile tubes for biochemical analysis and measurement of serum cortisol concentration and into an ethylenediaminetetraacetic acid (EDTA) tube for measurement of the complete blood count. Blood samples for serum biochemistry and cortisol were centrifuged and the serum was extracted and stored frozen until

laboratory analysis within 2 wk. Blood samples in EDTA were placed on ice and analyzed for complete blood cell profiles within 3 hr. Blood was analyzed on a biochemistry analyzer (Abbott Spectrum® Series II, Abbott Laboratories Diagnostic Division, Abbott, Abbott Park, Illinois, USA) and a hematology analyzer (Abbott Cell-Dyn® 3200, Abbott Laboratories Diagnostic Division).

To quantify the analgesic effects of XZT and ZT, the pulse rate and mean arterial pressure (MAP) were recorded at 20 and 50 min after administration of each drug. Hemostats were then applied with full compression to the base of the lateral-most claw on the right forelimb for 10 sec immediately after baseline measurements. Pulse rate and MAP was then recorded again 20 sec after removal of the hemostat. Any significant increase in pulse rate or MAP was interpreted as a response to pain, with the magnitude of change correlated directly with the amount of pain perceived.

One hour after drug administration, all physiologic monitors were disconnected and the bear was weighed on a platform overlying electronic load bars (Senstek, Norac Systems, Saskatoon, Saskatchewan, Canada). Bears receiving XZT were administered tolazoline (Tolazine®, Lloyd Laboratories, Shenandoah, Iowa, USA) at twice the xylazine dosage with half the dose given intravenously and the other half given intramuscularly. Bears receiving ZT were allowed to recover undisturbed.

The immobilization and handling protocol for captive polar bears was approved through the Animal Care Committee at the University of Saskatchewan (protocol number 980036).

Free-ranging polar bears

Seventeen free-ranging polar bears were located from a helicopter along the west coast of Hudson Bay near Churchill (57°00'–58°50'N, 92°25'–94°15'W) in August 2001. They were immobilized from the helicopter using remote injection (Cap-Chur®, Palmer Equipment Co., Douglasville, Georgia, USA) with XZT administered as X (Cervizine 300®, Wildlife Pharmaceuticals, Inc., Fort Collins, Colorado, USA) and ZT in a 2:3 combination by weight at an induction dose of 5–6 mg/kg based on estimated body weight. The drug was prepared as a solution (300 mg/ml) by adding 1.1 ml of X (300 mg/ml) and 1.3 ml of sterile water for injection to 500 mg of lyophilized ZT, resulting in a final volume of 2.8 ml per vial. The lyophilized drug powder contributed approximately 0.4 ml to the final volume.

Pulse and respiratory rates, SpO₂, and rectal temperature were recorded at 15 min following

drug administration, and every 10 min afterwards during 45 min of handling. At the conclusion of handling, bears were administered either yohimbine (Antagonil®, Wildlife Pharmaceuticals, Inc.) at 0.2 mg/kg, or atipamezole (Antisedan®, Orion Corporation, Animal Health, Turku, Finland) at 0.15 mg/kg, with half the dose given intravenously and the other half given intramuscularly. Tolazoline was not administered to free-ranging polar bears because it had proven ineffective with captive bears during earlier testing of XZT.

The capture and handling protocol for free-ranging polar bears was approved through the Canadian Wildlife Service, Prairie and Northern Region, Animal Care Committee (protocol number 2001PNR013).

Statistical analyses

All data were analyzed using SPSS® 10.0 for Windows® (SPSS Inc., Chicago, Illinois). Two-way analysis of variance (ANOVA) for repeated measures was used to compare physiologic measures between drugs (XZT versus ZT), between captive bears and free-ranging bears immobilized with XZT, and among time points following drug administration (Zar, 1996). Hematology and serum biochemistry values were compared between drug treatments using paired *t*-tests. To assess analgesic effect within each drug treatment, one-sample *t*-tests were used to determine if change in physiologic measures and blood gas values differed significantly from zero. Where assumptions of parametric statistics were violated, data were transformed to their natural logarithm and analyzed accordingly. Statistical significance was assigned when the probability (*P*) of Type I error was ≤0.05. All results are reported as the mean ± standard error (SE).

RESULTS

Captive polar bears

Although induction time was similar between drugs, induction dosage and volume were less with XZT (Table 1). There was no correlation between induction time and dosage with either combination (Spearman rank correlation: ZT— $r_s=0.03$, $P=0.93$; XZT— $r_s=0.36$, $P=0.34$). Dosages based on measured body weight ranged almost two-fold with each combination (Table 1). The time to reverse the effects of XZT immobilization with tolazoline was prolonged (>22 min) and did not appear to differ

TABLE 1. Anesthetic characteristics^a of captive polar bears receiving either xylazine-zolazepam-tiletamine (XZT) or zolazepam-tiletamine (ZT).

Drug	n	Induction			Reversal ^b
		Time (min)	Dosage (mg/kg)	Volume (ml/300 kg)	Time (min)
XZT	9	4.1 ± 0.9 (1.5–10.5)	4.8 ± 0.3*** (2.7–5.6)	6.5 ± 0.4*** (3.7–7.6)	33.9 ± 1.6 (22.5–70.5)
ZT	9	5.7 ± 1.4 (2.3–15.3)	7.2 ± 0.5*** (5.3–9.5)	9.5 ± 0.7*** (7.0–12.6)	NA

^a Results presented as mean ± standard error with minimum and maximum values in brackets. “***” indicates a significant difference ($P \leq 0.001$) between drug combinations, NA = not applicable.

^b Anesthesia with XZT was reversed with tolazoline at 3.8 ± 0.6 mg/kg with half the volume given intravenous and the other half given intramuscular.

from time for recovery without antagonist following ZT immobilization.

Bears immobilized with XZT had slower pulse rates and higher mean arterial pressures than bears immobilized with ZT (Fig. 1). There was no significant difference in rectal temperature between drug groups (Fig. 1). Nevertheless, rectal temperature increased over time in bears immobilized with XZT (repeated measures ANOVA: $F=7.1$, $P \leq 0.01$) and decreased over time in bears immobilized with ZT ($F=13.3$, $P \leq 0.001$).

Respiratory rates and minute volumes were similar between drug combinations (Fig. 1). However, bears immobilized with XZT had lower arterial oxygen tension (P_{aO_2}), SpO_2 , and blood pH than bears immobilized with ZT (Figs. 1, 2). Arterial oxygen tension (XZT— $F=16.5$, $P \leq 0.001$; ZT— $F=6.9$, $P \leq 0.01$) and SpO_2 (XZT— $F=7.4$, $P \leq 0.001$; ZT— $F=6.6$, $P \leq 0.01$) increased over time with both combinations. In bears immobilized with ZT, arterial carbon dioxide tension ($F=5.1$, $P \leq 0.01$) decreased and arterial blood pH ($F=5.3$, $P \leq 0.01$) increased over time.

Many hematologic values were greater in bears immobilized with XZT (paired t -test, $p \leq 0.05$ for the following variables: red blood cells— $7.0 \pm 0.12 \times 10^{12}/l$ vs. $6.5 \pm 0.28 \times 10^{12}/l$; hemoglobin— 166 ± 1.3 g/l vs. 150 ± 3.9 g/l; packed cell volume— 47 ± 0.5 l/l vs. 43 ± 0.2 l/l; platelets— $365 \pm 30.6 \times 10^9/l$ vs. $250 \pm 33.0 \times 10^9/l$; and white blood cells— $5.9 \pm 0.49 \times 10^9/l$ vs.

$5.0 \pm 0.51 \times 10^9/l$). Nevertheless, there were no differences in the proportions of different white cell populations between drugs. Serum concentrations of potassium (4.0 ± 0.09 mmol/l vs. 3.5 ± 0.05 mmol/l), glucose (10.1 ± 0.44 mmol/l vs. 6.7 ± 0.19 mmol/l), creatinine (121 ± 9.5 μ mol/l vs. 105 ± 6.9 μ mol/l), and albumin (32 ± 0.5 g/l vs. 31 ± 0.6 g/l) were also greater in bears immobilized with XZT (paired t -test, $P \leq 0.05$).

Pulse rate and mean arterial pressure increased in bears immobilized with ZT immediately following the compression of a claw with hemostats but did not change in bears immobilized with XZT (Fig. 3).

Free-ranging polar bears

Induction dosages (based on estimated body weight) and times with XZT were similar between free-ranging and captive bears (mean ± standard deviation: dose— 5.5 ± 1.81 mg/kg vs. 4.8 ± 0.95 mg/kg, $t=0.99$, $P=0.34$; time— 4.5 ± 1.29 min vs. 4.1 ± 2.81 min, $t=0.53$, $P=0.60$). Induction dosages ranged from 3.0–15.3 mg/kg. There was no significant correlation between induction time and dosage (Pearson correlation: $r=0.39$, $P=0.12$, $n=17$). Physiologic values following the administration of XZT were similar between free-ranging and captive bears (Fig. 1). Full reversal of XZT immobilization was not induced with either yohimbine or atipamezole, and all animals remained recumbent 15 min following drug administration.

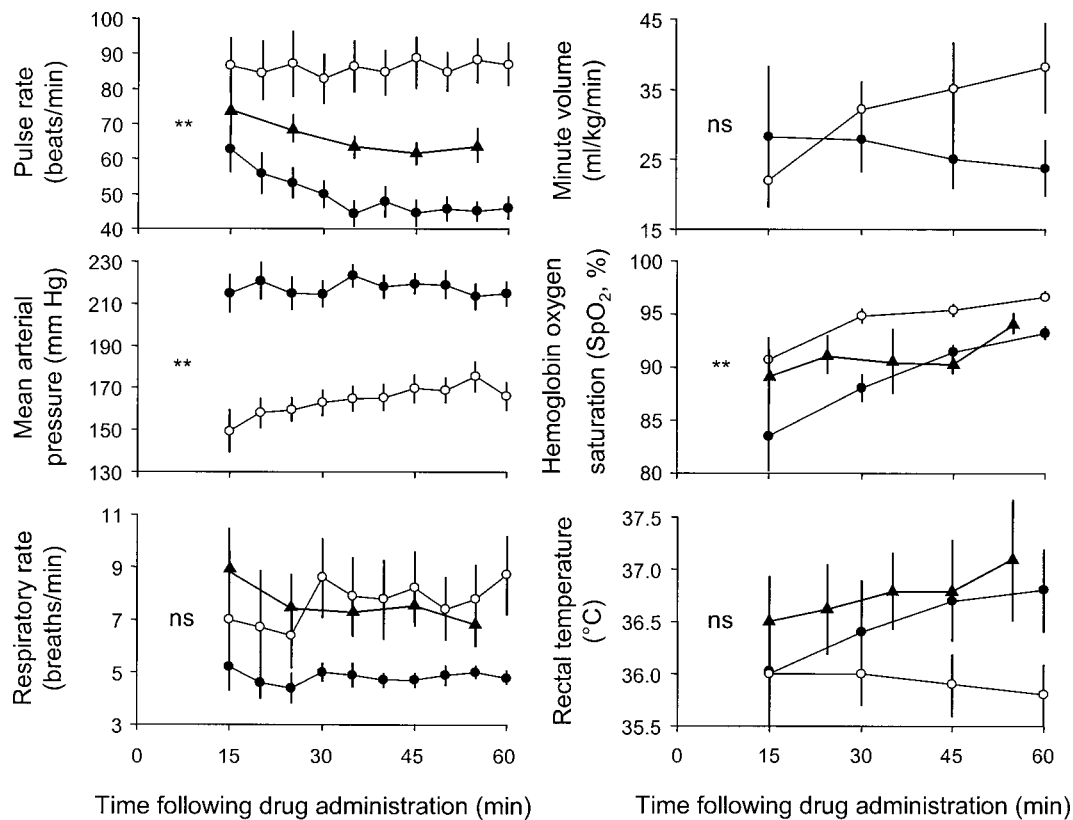


FIGURE 1. Physiologic responses of nine captive polar bears during immobilization with XZT (●) and with ZT (○), and 17 free-ranging polar bears during immobilization with XZT (▲). Means and standard error bars are shown. Differences between drug treatments over time in captive bears are indicated by “**” for $P \leq 0.01$, or “ns” for non-significant. No significant differences were observed in any of the measured responses between captive bears and free-ranging bears immobilized with XZT. SpO_2 increased over time in captive bears during immobilization with XZT ($P \leq 0.001$) and with ZT ($P \leq 0.01$). Rectal temperature changed over time in captive bears, increasing during XZT immobilization ($P \leq 0.01$) and decreasing during ZT immobilization ($P \leq 0.001$).

Although most free-ranging bears recovered uneventfully from immobilization, a 9-yr old female died approximately 24 hr following the administration of XZT and atipamezole. Serum collected within 30 min of XZT administration contained high concentrations of total bilirubin (76 $\mu\text{mol/l}$), alanine aminotransferase (76 U/l), aspartate aminotransferase (1120 U/l), and γ -glutamyltransferase (183 U/l). A necropsy was performed within 1 hr following death with the major finding being marked pallor of all visceral organs. Subsequent histologic examination of collected tissues revealed a generalized paucity of cells in

blood vessels and diffuse multifocal hepatic necrosis and pericholangiohepatitis.

DISCUSSION

Polar bears were immobilized effectively with XZT at an average dosage of 4.8 mg/kg (i.e., X at 1.9 mg/kg + ZT at 2.9 mg/kg) in captivity and at an average dosage of 5.5 mg/kg (i.e., X at 2.2 mg/kg + ZT at 3.3 mg/kg) when free-ranging. In addition, XZT was safe at two to three times greater than the mean dosage.

In general, induction of immobilization with XZT was predictable and smooth, muscle relaxation was good, and all bears

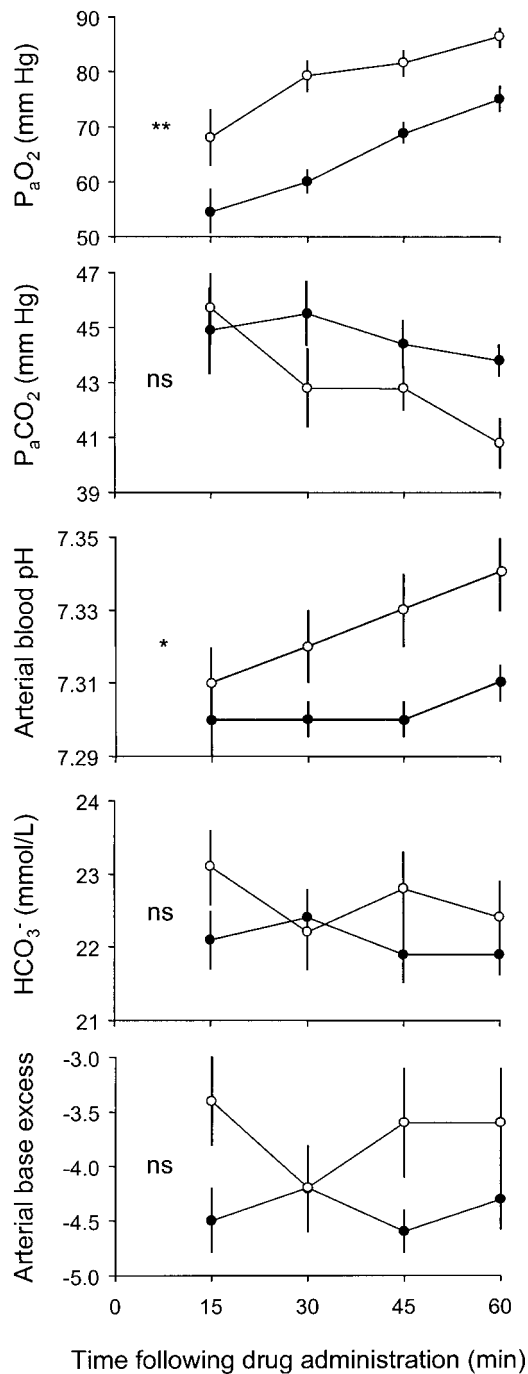


FIGURE 2. Blood gas values for nine captive polar bears during immobilization with XZT (●) and with ZT (○). Means and standard error bars are presented. Differences between drug treatments over time are indicated by '*' for $P \leq 0.05$, '**' for $P \leq 0.01$, and 'ns' for non-significant. P_aO_2 increased over time during immobilization with XZT ($P \leq 0.001$) and with ZT ($P \leq 0.01$). P_aCO_2 decreased ($P \leq 0.01$) and arterial pH

remained completely immobilized and unresponsive to stimuli throughout the immobilization period. However, behavioral effects of XZT during induction were different than with ZT. Ataxia was not always apparent, as bears often remained standing still for a time before sinking into recumbency. Further, in contrast to ZT, bears administered XZT could not be approached safely while still able to raise their head. Some bears that were approached while still able to raise their head also were able to return to standing with some difficulty and move toward or away from field personnel. Delaying approach toward an immobilized bear until a minute or two after its head was down increased safety greatly.

Relative to ZT XZT was delivered in smaller volumes. The preparation of XZT with concentrated X permitted delivery of a volume that was approximately 45% of that required if ZT was administered alone. Thus for example, where a 10 ml dart would be required to deliver enough ZT to immobilize a 300 kg polar bear (based on the drug concentration and dose used for this study), only a 5 ml dart would be required to deliver an effective volume of XZT. The smaller volumes required with XZT enable the use of slow-injection dart systems (air or gas pressurized darts) instead of the more traumatic rapid-injection systems (darts with explosive internal charges) that are commonly used for drug volumes >6 ml. Although slow-injection dart systems were not used in this study, they have proven reliable in previous studies of polar and grizzly bears using both XZT and medetomidine-ZT (MZT) under a wide range of ambient temperatures (-10 to 20 °C; Cattet et al., 1999, 2003).

Bears immobilized with XZT had slower pulse rates and higher mean arterial pressures than bears immobilized with ZT.

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increased ($P \leq 0.01$) over time during immobilization with ZT.

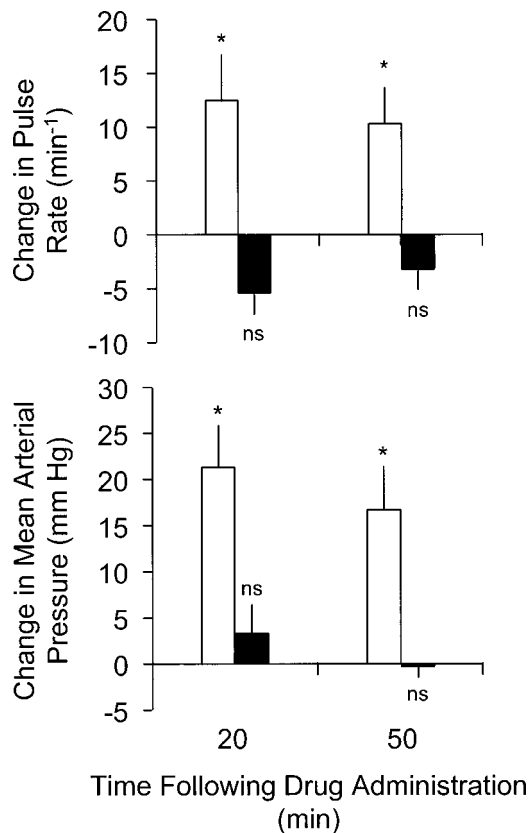


FIGURE 3. Change in heart rate and mean arterial pressure of nine captive polar bears after clamping the claw bed with a hemostat during immobilization with XZT (closed box) and ZT (open box). Boxes indicate mean change with standard error bar at 20 sec after clamping at 20 min and 50 min following drug administration. Changes in heart rate and arterial pressure at each time are indicated by '*' for $P \leq 0.05$ and 'ns' for non-significant.

Pulse rates also tended to be slower in captive bears than in free-ranging bears. Similar pulse rates have been reported in polar bears following immobilization with MZT (Cattet et al., 1997, 1999), and in non-anesthetized, resting polar bears (Øritsland, 1970). High mean arterial pressures likely resulted from increased vascular resistance caused by X (Kline and Klide, 1989). However, ZT may have also affected blood pressure through stimulation of the sympathetic nervous system (Hellyer et al., 1988; Lin et al., 1989). Similarly high values have also been reported

for polar bears immobilized with MZT (Caulkett et al., 1999).

Rectal temperature increased slowly over time (~ 0.5 C per hr) following immobilization with XZT (Fig. 1), a pattern that was evident over a wide range of ambient temperatures (-10 to 18 C). The cause for this rise in temperature is unknown; it may be that the dissipation of body heat was impaired by the X-induced vasoconstriction of peripheral blood vessels (Doherty, 1988; Kline and Klide, 1989). Whatever the underlying mechanism, the slow rise in body temperature was not significant enough to cause hyperthermia, but could inhibit the effective cooling of an already hyperthermic animal.

Although respiratory rates and minute volumes were similar between bears immobilized with XZT and those immobilized with ZT, the blood gas data indicated the P_aO_2 was less with XZT. It improved over time, but was at hypoxemic values (≤ 60 mm Hg) in some bears during the first 30 min following drug administration. Hypoxemia was probably due to increased venous admixture from ventilation-perfusion (V/Q) mismatch. Increased pulmonary venous admixture resulting in V/Q mismatch contributed to hypoxemia during medetomidine-ketamine immobilization in sheep (Caulkett et al., 1996). Similar changes in P_aO_2 were found in polar bears immobilized with MZT (Caulkett et al., 1999). Where hypoventilation typically increases arterial carbon dioxide tension (P_aCO_2) and decreases P_aO_2 , the P_aCO_2 values for polar bears immobilized with XZT were normal, e.g., 35–45 mm Hg. Further, P_aCO_2 values did not differ between drug combinations, and yet oxygenation was good with ZT. This suggests that hypoventilation contributed little to hypoxemia during immobilization with XZT.

Arterial pH, bicarbonate (HCO_3^-), and base excess (BE) values were slightly lower in immobilized polar bears than would be expected under normal conditions (pH=7.4, HCO_3^- =25 mmol/l, and BE=0) and likely reflect an overall increase in an-

aerobic metabolism. This mild acidosis improved with time in bears immobilized with ZT, but remained unchanged in bears immobilized with XZT. Similarly, bears immobilized with MZT developed a mild acidosis that persisted throughout a 1 hr period following drug administration (Caulkett et al., 1999).

Together, the physiologic and blood gas data provide evidence to indicate oxygen delivery to tissues was lower during immobilization with XZT than with ZT. Sheep immobilized with medetomidine-ketamine demonstrate similar depression in heart rate and increase in blood pressure (Caulkett et al., 1996). They also show a significant decrease in cardiac output and oxygen delivery when compared to baseline values prior to immobilization. Although oxygen delivery appears to be reduced in polar bears immobilized with XZT, the disturbance to physiologic function and blood gas values is not severe enough to compromise the health of most bears. There is potential, however, for bears with pre-existing disease to experience problems with XZT. In these animals, the provision of supplemental oxygen by intranasal route helps to prevent or treat hypoxemia (Read et al., 2001; Cattet et al., 2003). Although medical grade oxygen is not a standard component of many field kits, a "D" size aluminum oxygen cylinder with mini-regulator and nasal cannula can be carried in the field under many environmental conditions with little difficulty and was used with some free-ranging bears in this study. This equipment provides an invaluable aid to assisting field anesthesia, especially when used in conjunction with a pulse oximeter and, in our opinion, should be included as a standard component of field gear.

Serum glucose concentrations in bears immobilized with XZT were almost two-fold greater than values measured in bears immobilized with ZT. This was likely caused by the effect of X at α_1 -adrenergic receptors to increase hepatic glucose production through glycogenolysis, and at α_2 -

adrenergic receptors to decrease the pancreatic release of insulin into the blood (Klein and Klide, 1989; Gross and Tranquilli, 1989).

All blood cell counts were greater in bears immobilized with XZT than in those immobilized with ZT. A plausible explanation is that plasma was forced from blood vessels into the surrounding tissue space as a result of the significant rise in arterial blood pressure following XZT administration. Accordingly, an imbalance of forces developed at the capillary membrane as mean capillary pressure increased (Guyton, 1986). The net force favored filtration of fluid from the capillaries into the surrounding tissue space. As a result, the blood concentration of cells and large molecules such as albumin increased.

Xylazine-zolazepam-tiletamine appeared to provide good analgesia because neither pulse rate nor MAP changed in response to painful stimulus. In contrast, significant increases in pulse rate and MAP were observed in bears immobilized with ZT, even at higher dosages >9 mg/kg. This reinforces observations made in a previous study in which it was concluded that ZT provided poor analgesia (Caulkett et al., 1999).

The effects of XZT immobilization were not reversed effectively or reliably with the α_2 -antagonist drugs tolazoline, yohimbine, or atipamezole. There wasn't any indication of reversal effects with tolazoline at 3.5–4.0 mg/kg and recovery times did not appear to differ from times observed in bears following ZT immobilization where no antagonist drug was administered. In contrast, partial reversal occurred in some bears (raising of head, purposeful movement of limbs) following administration of atipamezole at 150 μ g/kg and, to a lesser extent, yohimbine at 200 μ g/kg. Further, physiologic responses to these drugs including increases in pulse and respiratory rates and reflex activity were often observed within minutes following injection. This suggests administration of atipamezole or yohimbine could provide effective treatment of potential adverse responses

during anesthesia with XZT, e.g., bradycardia, hypoxemia, and hyperthermia. Lack of complete reversibility (i.e., return to standing) may be particular to polar bears captured during fall. At this time of year, many polar bears are fasting and in a depressed metabolic state; rectal temperatures as low as 33.5 C are not an uncommon finding (Cattet, 2000). In such a state, it is conceivable that drug metabolism could be reduced to the extent that a low dose of ZT (3–5 mg/kg) may be sufficient to maintain some polar bears in an immobilized state even after the effects of X have been reversed. Xylazine-zolazepam-tiletamine has not been administered to polar bears during other times of the year when their metabolic rate is higher. However, it has been administered to grizzly bears under normal metabolic conditions (feeding and rectal temperature ≥ 37 C) and, in this species, the effects of XZT were reversed more effectively by yohimbine (Cattet et al., 2003). As well, MZT has been administered to free-ranging fasting polar bears captured during summer and fall and the effects of MZT (medetomidine at 60 $\mu\text{g/kg}$ + ZT at 2 mg/kg) could be reversed safely and reliably with atipamezole at 240 $\mu\text{g/kg}$ (Cattet et al., 1997).

The results of serum biochemistry, necropsy, and histopathology on the female polar bear that died following immobilization with XZT were consistent with marked anemia and severe liver disease, pathologic processes of chronic duration (>1 wk) that were not caused by XZT or other elements of the handling process. Instead, it seems the compromised health of this animal prevented its successful recovery from the additional physiologic stresses imposed by capture and handling.

In conclusion, polar bears can be immobilized effectively and reliably with XZT at a dosage of 4–6 mg/kg (with a 2:3 ratio of X to ZT). This combination is tolerated safely by polar bears at two to three times the recommended dose, but relative to ZT the physiologic effects of immobili-

zation with XZT are more pronounced. High blood pressure ($\text{MAP} \geq 200$ mm Hg) and transient hypoxemia ($\text{P}_a\text{O}_2 \leq 60$ mm Hg) immediately following immobilization are common findings, but these conditions do not appear to pose significant risk to healthy bears. Xylazine-zolazepam-tiletamine provided analgesia superior to ZT and is preferable for painful procedures such as tooth extraction or tissue biopsy. For polar bears, the effects of immobilization with XZT cannot be reversed with the α_2 -antagonist drug tolazoline. However, they can be reversed to some extent with yohimbine or atipamezole, but the time to complete reversal of effects is highly variable among bears.

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