

Anesthesia of grizzly bears using xylazine–zolazepam–tiletamine or zolazepam–tiletamine

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Abstract: The immobilization features and physiological effects of combinations of xylazine–zolazepam–tiletamine (XZT) and zolazepam–tiletamine (ZT) were compared in 46 wild grizzly bears (*Ursus arctos*) handled during 90 captures. Although induction time was similar between drugs, induction dosage and volume were less with XZT than with ZT. Induction of immobilization with XZT was predictable and smooth, and muscle relaxation was good during the period of immobilization. XZT was tolerated safely at 2–3 times the recommended dosage of 6–7 mg/kg (xylazine at 2.4–2.8 mg/kg + ZT at 3.6–4.2 mg/kg with X and ZT mixed in a 2:3 ratio). Bears anesthetized with XZT had slower pulse rates and higher rectal temperatures than bears anesthetized with ZT. The risk of hyperthermia at higher ambient temperatures ($\geq 25^{\circ}\text{C}$) was of potential concern with XZT. Although transient hypoxemia (hemoglobin oxygen saturation $[\text{SpO}_2] \leq 85\%$) developed immediately following induction in some bears, it was not severe enough to pose significant health risk. The provision of supplementary oxygen during hypoxemia resulted in increased SpO_2 and decreased pulse rate. Bears anesthetized with XZT had higher serum glucose concentrations than bears anesthetized with ZT, a finding likely explained by the α_2 -adrenergic effects of xylazine to increase hepatic glucose production and decrease pancreatic release of insulin. Although the time to complete reversal of effects was highly variable, the effects of XZT anesthesia could be reversed with the α_2 -antagonist drug yohimbine.

Key words: anesthesia, grizzly bear, Telazol[®], tiletamine, *Ursus arctos*, xylazine, yohimbine, zolazepam

Ursus 14(1):88–93 (2003)

A 1:1 mixture of zolazepam and tiletamine (Telazol[®] or Zoletil[®]) 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 are that its anesthetic effects are highly predictable, it causes minimal depression of physiological 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, zolazepam–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 pain-killing (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 anesthetized with ZT may have prolonged recoveries lasting many hours, especially if multiple doses of ZT 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 anesthetize brown, polar (*U. maritimus*), and black bears (*U. americanus*) (Cattet et al. 1997, Caulkett and Cattet

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1997, Röken 1997, Arnemo 2001). The combination is administered at approximately 25% of the volume required for ZT alone. Further, medetomidine has potent analgesic effects 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 as a concentrated solution (i.e., >1 mg/ml).

In recent years, another α_2 -agonist drug, xylazine, has been used in combination with ZT to anesthetize a variety of wildlife (Millspaugh et al. 1995, Sweitzer et al. 1997, Galka et al. 1999, Caulkett et al. 2000), including polar bears (Cattet et al. 2003a). In contrast to medetomidine, xylazine is relatively inexpensive, available widely, and has been used routinely for wildlife chemical immobilization. Here, data are presented from free-ranging grizzly bears to compare the immobilization features and physiological effects of xylazine-zolazepam-tiletamine (XZT) and zolazepam-tiletamine (ZT) and to determine the effectiveness of the α_2 -antagonist yohimbine to reverse anesthesia with XZT.

Study area and methods

Forty-six free-ranging grizzly bears were handled during 90 captures that occurred in west-central Alberta (52°40'–53°60'N and 116°50'–118°00'W) between April 1999 and August 2001, as part of the Foothills Model Forest Grizzly Bear Research Project. Bears were either located from a helicopter or captured by leg-hold snare (Jonkel and Cowan 1971) and anesthetized using remote injection (Pneudart® Inc., Williamsport, Pennsylvania, USA and Paxarms® N.Z. Ltd., Timaru, New Zealand). The capture and handling protocol was approved through the Animal Care Committee at the University of Saskatchewan (protocol number 19990023).

For 36 captures, bears were anesthetized with zolazepam-tiletamine (ZT) (Telazol®, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa, USA) at an induction dosage of 8–10 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 each glass vial containing 500 mg of lyophilized Telazol®, resulting in a final volume of 2.2 ml/vial. The lyophilized drug powder contributed approximately 0.4 ml to the final volume, hence the greater volume of drug solution than added water.

For the remaining 54 captures, bears were anesthetized with xylazine-zolazepam-tiletamine (XZT) consisting of xylazine (Cervizine 300®, Wildlife Phar-

maceuticals, Inc., Fort Collins, Colorado, USA) and Telazol® in a 2:3 combination by weight at an induction dosage of 6 mg/kg (2.4 mg/kg xylazine + 3.6 mg/kg ZT) based on estimated body weight. The drug was prepared as a solution (332 mg/ml) by adding 1.1 ml of xylazine (300 mg/ml) and 1.0 ml of sterile water for injection to each glass vial containing 500 mg of lyophilized Telazol®, resulting in a final volume of 2.5 ml/vial. Again, the lyophilized drug powder contributed approximately 0.4 ml to the final volume.

Pulse and respiratory rates and rectal temperature (Excel 10® digital thermometer, AMG Medical, Montreal, Quebec, Canada) were recorded for all bears at the onset of handling and every 15 min afterward during the 75 min of handling. For some bears anesthetized with XZT, percent hemoglobin saturation (SpO₂; 4402 Vet/Ox pulse oximeter system, Sensor Devices, Waukesha, Wisconsin, USA) was also measured. Bears showing clinical signs of hypoxemia (blue-tinged mucous membranes or SpO₂ ≤ 85%) were administered medical grade oxygen by intranasal route (6–10 L/min) until signs improved. To determine actual drug dosages, bears were weighed in a sling suspended beneath a load scale (MSI-7200 Dynalink, Precision Giant Systems Inc., Edmonton, Alberta, Canada).

Blood was collected from the medial saphenous vein into sterile tubes for biochemical analysis and into an EDTA (ethylenediamine tetra acetic acid) tube for measurement of the complete blood count. Blood samples for serum biochemistry were centrifuged and the serum was extracted and stored frozen (–18°C) until laboratory analysis (within one month) using an Abbott Spectrum® Series II biochemistry analyzer (Abbott Laboratories Diagnostic Division, Abbott Park, Illinois, USA). Blood samples in EDTA were chilled and analyzed for complete blood cell profiles within 24 hrs using an Abbott Cell-Dyn® 3200 hematology analyzer (Abbott Laboratories Diagnostic Division, Abbott Park, Illinois, USA). At the conclusion of handling, bears anesthetized with XZT were administered yohimbine (Antagonil®, Wildlife Pharmaceuticals, Inc., Fort Collins, Colorado, USA) intramuscularly, or half volume intramuscularly and half volume intravenously, at 0.15–0.20 mg/kg.

All data were analyzed using SPSS® 10.0 for Windows® (SPSS Inc., Chicago, Illinois, USA). Three-way ANOVA for repeated measures was used to compare physiological measures between drugs (XZT vs. ZT), between methods of capture (helicopter vs. leg-hold snare), and among time points following drug administration (Zar 1996). Two-way ANOVA was used to compare hematology and serum biochemistry values between

Table 1. Anesthetic characteristics of grizzly bears receiving either xylazine–zolazepam–tiletamine (XZT) or zolazepam–tiletamine (ZT) for a study conducted in west-central Alberta between April 1999 and August 2001.

Drug	n	Induction ^a			Reversal ^b
		Time (SD) min	Dosage ^c (SD) mg/kg	Volume (SD) ml/200 kg	Time (SD) min
XZT	54	6.2 (0.5)	6.7 (0.5)***	3.9 (0.3)***	19.7 ± 2.9
Median		5.0	6.3	3.7	15.0
Range		2.0–18.0	3.2–16.3	1.9–9.6	2.0–64.0
ZT	36	6.3 (0.6)	9.7 (0.9)***	8.5 (0.8)***	–
Median		5.0	9.2	8.1	
Range		2.0–18.0	5.3–18.2	4.7–16.0	

*** indicates a significant difference ($P \leq 0.001$) between drug combinations.

^bAnesthesia with XZT was reversed by a single injection of yohimbine (mean dose = 0.19 mg/kg, SD = 0.014) administered intramuscularly, or half intravenously and half intramuscularly.

^cIndividual dosages for xylazine (X) and Telazol[®] (ZT) components of XZT are: mean = 2.7 mg/kg X + 4.0 mg/kg ZT; median = 2.5 mg/kg X + 3.8 mg/kg ZT; and range = 1.3–6.5 mg/kg X + 1.9–9.8 mg/kg ZT.

drugs and between methods of capture. Julian date-of-capture was included as a covariate in all analyses. 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 a Type I error was ≤ 0.05 .

Results

Although induction time was similar between drugs, induction dosage and volume were less with XZT than with ZT (Table 1). There was no significant correlation between induction time and induction dosage with either drug combination (Pearson correlation: XZT – $r = 0.04$, $P = 0.83$; ZT – $r = 0.29$, $P = 0.23$). Dosages based on measured body mass ranged almost four-fold with each drug combination (Table 1). The time to reverse anesthesia with XZT using yohimbine was highly variable and did not correlate with induction dosage ($r = -0.08$, $P = 0.62$). Although immobilization features were also affected by the method of capture, these results are presented elsewhere (Cattet et al. 2003b).

Bears anesthetized with XZT had slower pulse rates and higher rectal temperatures than bears anesthetized with ZT (Fig. 1). Respiratory rates were similar between drug combinations. The median of percent hemoglobin saturation (SpO_2) values recorded for 16 bears at random times between 15–60 min following the induction of anesthesia with XZT was 91% (range: 46–100%, $n = 44$ recordings).

Medical grade oxygen was administered by intranasal route (6–10 L/min) to 9 bears that showed clinical signs of hypoxemia (blue-tinged mucous membranes or $SpO_2 \leq 85\%$) following anesthesia with XZT. When

comparing values of SpO_2 and pulse rate measured within 10 min before and 10 min after the initiation of oxygen therapy, SpO_2 tended to increase (before = 79%, SD = 16; after = 86%, SD = 11; Wilcoxon signed ranks test – $Z = -1.75$, $P = 0.07$, $n = 7$) and pulse rate tended to decrease (before = 68 beats/min, SD = 17; after = 61 beats/min, SD = 13; Wilcoxon signed ranks test – $Z = -1.69$, $P = 0.09$, $n = 9$).

Mean corpuscular volume was less in bears anesthetized with XZT than in bears anesthetized with ZT (mean = 72 fL [femtoliter, 10^{-15} liters], SD = 0.7 versus mean = 75 fL, SD = 1.4 fL; 2-way ANOVA – $F = 6.38$, $df = 1$, $P = 0.01$). Serum concentrations of sodium (mean = 140 mmol [millimoles]/L, SD = 5.9 versus mean = 144 mmol/L, SD = 4.0; 2-way ANOVA – $F = 8.37$, $df = 1$, $P = 0.005$), chloride (mean = 104 mmol/L, SD = 8.3 versus mean = 110 mmol/L, SD = 5.4; 2-way ANOVA – $F = 15.51$, $df = 1$, $P \leq 0.001$), and lipase (mean = 262 U [International units]/L, SD = 109 versus mean = 330 U/L, SD = 153; 2-way ANOVA – $F = 4.15$, $df = 1$, $P = 0.04$) were less, and serum concentration of glucose (mean = 8.6 mmol/L, SD = 3.18 versus mean = 6.2 mmol/L, SD = 1.42; 2-way ANOVA – $F = 24.23$, $df = 1$, $P \leq 0.001$) was greater in bears anesthetized with XZT. Although physiological measures and blood values were also affected by method of capture, these results are presented elsewhere (Cattet et al. 2003b).

Discussion

Grizzly bears were anesthetized effectively with xylazine–zolazepam–tiletamine (XZT) at a mean dosage of 6.7 mg/kg (or xylazine at 2.7 mg/kg + Telazol[®] at 4.0 mg/kg). This is greater than the dosage required for

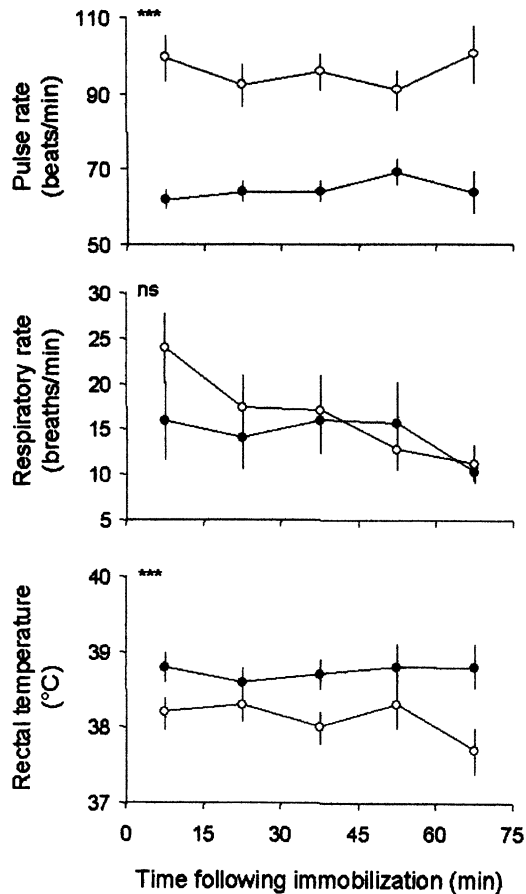


Fig. 1. Physiologic responses (means with standard error bars) of grizzly bears during anesthesia with XZT (●; $n = 54$) and with ZT (○; $n = 36$) for a study conducted in west-central Alberta between April 1999 and August 2001. Differences between drug treatments over time are indicated by “***” for $P < 0.001$ or “ns” for non-significant. No significant changes in physiological measurements occurred over time with either drug.

polar bears (4.8–5.5 mg/kg; Cattet et al. 2003a), indicating either the body weights of grizzly bears were more often over-estimated when compared to the body weights of polar bears or species differences exist in the sensitivity to this drug. XZT was tolerated safely by grizzly bears at dosages 2–3 times the mean dosage.

In general, induction of anesthesia with XZT was predictable and smooth, and muscle relaxation was good throughout immobilization. However, behavioral effects with XZT during induction were different than with ZT. Ataxia was not always apparent, as bears often remained standing for a time before sinking slowly into recumbency. Further, in contrast to ZT, bears administered

XZT could not be approached safely until they were unable to raise their head.

Relative to ZT, XZT was delivered in smaller volumes. The preparation of XZT with concentrated xylazine (300 mg/ml, Cervizine 300[®]) permitted the drug combination to be delivered in a volume that was approximately 45% of that required if ZT was administered alone. Further, the small volumes of XZT required to anesthetize most grizzly bears could be administered using 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 >5 ml.

The preparation of XZT as a solution at concentrations greater than that used in this study would be difficult. In fact, the concentration of 332 mg/ml (133 mg/ml xylazine + 199 mg/ml Telazol[®]) approached the threshold between a true solution and a suspension, and at lower temperatures (<10°C) it was difficult to maintain the drug in solution. XZT has been prepared at 300 mg/ml (120 mg/ml xylazine + 180 mg/ml Telazol[®]) for use in free-ranging polar bears by adding 1.1 ml of Cervizine 300[®] (xylazine at 300 mg/ml) and 1.3 ml of sterile water for injection to each glass vial containing 500 mg of lyophilized Telazol[®], resulting in a final volume of 2.8 ml per vial (Cattet et al. 2003a). At this concentration, the drug remained in solution at lower temperatures and the volume administered to bears was still approximately half that required when using Telazol[®] alone.

Bears anesthetized with XZT had a slower pulse than bears anesthetized with ZT (Fig. 1). Similar pulse rates of 40–70 beats/minute have been reported in polar bears anesthetized with XZT (Cattet et al. 2003a). Percent hemoglobin saturation (SpO_2) was recorded only sporadically in bears anesthetized with XZT because of limited opportunity to record values. Nevertheless, SpO_2 values were similar in grizzly bears to values reported for polar bears anesthetized with XZT (Cattet et al. 2003a) and indicate that transient hypoxemia ($SpO_2 \leq 85\%$) during the initial period of anesthesia may develop in some grizzly bears. The increase in SpO_2 and decrease in pulse rate following provision of supplemental oxygen suggest that oxygen therapy may be effective at treating hypoxemia, as has been demonstrated in elk (*Cervus elaphus*) anesthetized with XZT (Read et al. 2001).

Although medical grade oxygen has not been used routinely for many field studies, a “D” size aluminum oxygen cylinder with mini-regulator and nasal cannula can be carried in the field under many conditions with little difficulty and used with minimal training. This

equipment is available from most ambulance supply companies and, in our opinion, should be included as standard field gear. The availability of medical grade oxygen provides an invaluable aid to assisting field anesthesia, especially when used in conjunction with a pulse oximeter.

Rectal temperatures were higher in bears anesthetized with XZT than in bears anesthetized with ZT. The cause for this difference is unknown; it may be that xylazine-induced vasoconstriction of peripheral blood vessels interfered with the dissipation of body heat (Doherty 1988). The use of α_2 -agonist drugs impairs thermoregulatory capabilities in a wide variety of animals (Klein and Klide 1989). Relative to ZT, the use of XZT in grizzly bears at higher ambient temperatures ($\geq 25^\circ\text{C}$) has potential to cause hyperthermia.

Serum glucose concentrations in bears anesthetized with XZT were notably greater than values measured in bears anesthetized with ZT. The effect of xylazine at α_1 -adrenergic receptors is 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). Other differences between drugs in serum biochemistry (sodium, chloride, and lipase) and mean corpuscular volume were small and could not be attributed directly to the different drug combinations.

The anesthesia induced by XZT could be reversed completely, but not consistently, with the α_2 -antagonist drug yohimbine. However, physiological responses to yohimbine, including increases in pulse and respiratory rates and reflex activity, were often observed within minutes following injection. This suggests administration of yohimbine would provide effective treatment of adverse responses during anesthesia with XZT, (e.g., bradycardia, hypoxemia, and hyperthermia). The time to complete reversal (bear was standing and able to ambulate) following yohimbine injection was highly variable, but in general appeared quicker in bears administered higher dosages (200–300 $\mu\text{g}/\text{kg}$) and in bears administered half the reversal drug dose by intravenous route and the other half by intramuscular route. The efficacy of yohimbine and possibly other α_2 -antagonist drugs, such as tolazoline or atipamezole, warrants further investigation in grizzly bears.

Management implications

Grizzly bears can be anesthetized effectively and reliably with XZT at a dosage of 6–7 mg/kg (xylazine at 2.4–2.8 mg/kg + ZT at 3.6–4.2 mg/kg with X and

ZT mixed in a 2:3 ratio). Relative to ZT, XZT is administered in smaller volumes and can be delivered by slow-injection dart systems (air or gas pressurized darts) instead of more traumatic rapid-injection systems (darts with explosive internal charges) commonly used for drug volumes >5 ml. Although XZT is tolerated by grizzly bears at 2–3 times the recommended dosage, its physiological effects are more pronounced than those of ZT. The risk of hyperthermia at higher ambient temperatures ($\geq 25^\circ\text{C}$) is greater with XZT. Further, transient hypoxemia ($\text{SpO}_2 \leq 85\%$) immediately following induction may develop in some bears. Although it should not pose significant health risk to most bears, hypoxemia can be treated with supplemental oxygen. As with the use of any anesthetic drug, routine monitoring of physiological function (pulse and respiratory rates, mucous membrane color, and rectal temperature) in the anesthetized animal throughout handling will significantly reduce the potential for complications to develop. For grizzly bears, the anesthesia induced by XZT can be reversed with the α_2 -antagonist drug yohimbine, but the time to complete reversal (standing and ambulatory) is highly variable.

Acknowledgments

This project was supported by the Foothills Model Forest, Alberta Sustainable Resource Development, Parks Canada, and the many funding sponsors of the Foothills Model Forest Grizzly Bear Research Program. Field assistants requiring special thanks include J. Bell, K. Christison, B. Goski, J. Lee, R. Munro, J. Saunders, M. Urquhart, and the many Alberta Conservation Officers and Jasper Park Wardens who assisted with the capture and handling of grizzly bears.

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Received: 4 December 2001

Accepted: 31 January 2003

Associate Editor: M.R. Johnson