EFFECTIVENESS OF ANTAGONISTS FOR TILETAMINE-ZOLAZEPAM/XYLAZINE IMMOBILIZATION IN FEMALE WHITE-TAILED DEER

Authors: Miller, Brad F., Muller, Lisa I., Doherty, Tom, Osborn, David A., Miller, Karl V., et al.

Source: Journal of Wildlife Diseases, 40(3) : 533-537

Published By: Wildlife Disease Association

URL: https://doi.org/10.7589/0090-3558-40.3.533

Journal of Wildlife Diseases, 40(3), 2004, pp. 533–537

EFFECTIVENESS OF ANTAGONISTS FOR TILETAMINE-ZOLAZEPAM/XYLAZINE IMMOBILIZATION IN FEMALE WHITE-TAILED DEER

Brad F. Miller,[1,4] Lisa I. Muller,[1,5] Tom Doherty,[2] David A. Osborn,[3] Karl V. Miller,[3] and Robert J. Warren[3]

[1] Department of Forestry, Wildlife and Fisheries, University of Tennessee, 274 Ellington Hall, Knoxville, Tennessee 37996, USA
[2] Department of Large Animal Medicine, University of Tennessee, Veterinary Teaching Hospital, Knoxville, Tennessee 37996, USA
[3] Warnell School of Forest Resources, University of Georgia, Athens, Georgia 30602, USA
[4] Present address: Warnell School of Forest Resources, University of Georgia, Athens, Georgia 30602, USA
[5] Corresponding author (email: lmuller@utk.edu)

ABSTRACT: A combination of tiletamine-zolazepam/xylazine (TZ/X) is effective in the chemical immobilization of white-tailed deer (*Odocoileus virginianus*); however, the lengthy duration of immobilization may limit its usefulness. From October to November 2002, 21 captive female deer were assigned randomly to an α_2 antagonist treatment to reverse xylazine-induced sedation (seven does per group). All deer were given 220 mg of TZ (4.5±0.4 mg/kg) and 110 mg of X (2.2±0.2 mg/kg) intramuscularly (IM). Antagonist treatments were either 200 mg of tolazoline (4.0±0.4 mg/kg), 11 mg of atipamezole (0.23±0.02 mg/kg), or 15 mg of yohimbine (0.30±0.02 mg/kg) injected, half intravenously and half subcutaneously, 45 min after the IM TZ/X injection. In addition, 10 other deer (five per group) were immobilized as before and then given tolazoline (200 mg) after 45 min, with either a carrier (dimethyl sulfoxide [DMSO]) or carrier (DMSO) plus flumazenil (5 mg) to reverse the zolazepam portion of TZ. Mean times from antagonist injection until a deer raised its head were different for α_2 antagonist treatments (P=0.02). Times were longer for yohimbine (62.3±42.7 min) than for either atipamezole (24.3±17.1 min) or tolazoline (21.3±14.3 min). Mean times from antagonist injection until standing were not different (P=0.15) among yohimbine (112.0±56.4 min), atipamezole (89.7±62.8 min), or tolazoline (52.6±37.2 min). A sedation score based on behavioral criteria was assigned to each deer every 30 min for 5 hr. On the basis of sedation scores, tolazoline resulted in a faster and more complete reversal of immobilization. Flumazenil treatment did not affect recovery.

Key words: Antagonist, atipamezole, flumazenil, immobilization, *Odocoileus virginianus,* Telazol®, tiletamine, tolazoline, white-tailed deer, xylazine, yohimbine, zolazepam.

INTRODUCTION

One of the most commonly recommended drug combinations for the remote immobilization of wild white-tailed deer (*Odocoileus virginianus*) is Telazol® (TZ) plus xylazine (X; Kreeger, 1996; Kilpatrick and Spohr, 1999). Deer have also been remotely immobilized using ketamine plus xylazine (K/X); however, shorter flight distances after darting and smaller search areas have been reported with the use of TZ/X vs. K/X (Kilpatrick and Spohr, 1999). Therefore, TZ/X greatly facilitates the capture of white-tailed deer and is effective and safe when it is administered under field conditions (Kilpatrick and Spohr, 1999; Murray et al., 2000). One problem with TZ/X immobilization is the extended recovery time for deer (Millspaugh et al., 1995; Nielsen, 1999; Miller et al., 2003). Prolonged TZ/X immobilization might lead to decreased survival of deer, which must respond quickly to dangerous environmental situations. Complications from extended immobilization may also cause concerns with sensitive darting situations in urban/suburban areas.

Telazol® is a combination of tiletamine (tiletamine hydrochloride) and zolazepam (zolazepam hydrochloride) in a 1:1 ratio (Haigh et al., 1985). Tiletamine is a cyclohexanone dissociative anesthetic with no known antagonist. Zolazepam, a benzodiazepine, has been successfully antagonized with flumazenil (FLU) and sarmazenil (Spelman et al., 1997; James et al., 1999; Walzer and Huber, 2002). There have been no published reports of the use of FLU or sarmazenil in white-tailed deer.

Xylazine is an α_2-andrenergic agonist

that is often used in combination with TZ. Although many α_2 antagonists have been used to reverse the effects of X, there have been few comparisons of these compounds for antagonizing X in white-tailed deer.

The purpose of the present study was to 1) identify the most effective α_2 antagonist for X reversal and 2) determine whether the addition of the benzodiazepine antagonist FLU would improve recovery from TZ/X immobilization in white-tailed deer.

METHODS AND STUDY AREA

All research was conducted at the University of Georgia Daniel B. Warnell School of Forest Resources Whitehall Deer Research Facility (33°53′N, 83°21′W). Research protocols received prior approval from the University of Tennessee and the University of Georgia Animal Care and Use Committees (UT-ACUC 1184; UGA-ACUC A3437-01).

Deer were housed in large (0.4–0.8 ha) outdoor pens with food (Antler King Trophy Products, Inc., Black River Falls, Wisconsin, USA) and water available ad libitum. Deer were moved to individual 3×6-m stalls 16–24 hr before treatments. Food was withheld from deer beginning 12–16 hr before chemical immobilization. Trials were conducted from October to November 2002.

To prevent any confounding effects of reproductive hormones from males during the rut, only adult females were used (2.5–12.5 yr old). Mean weights (±SD) of the deer were 49.7±4.7 kg. Each deer was manually restrained in a squeeze chute and was given 220 mg of TZ (100 mg/ml; Fort Dodge Animal Health, Fort Dodge, Iowa, USA) and 110 mg of X (Cervizine; Wildlife Pharmaceuticals, Inc., Fort Collins, Colorado, USA) via intramuscular (IM) injection into the hindquarters (modified from Miller et al., 2003). Immediately after drug injection, deer were released into a 15×20-m observation pen, and the times (min) to first noticeable drug effect, sternal recumbency, and lateral recumbency were recorded. Once recumbent, each deer was carried to a centralized examination area and treated with ophthalmic ointment (Paralube® Vet Ointment; Pharmaderm, Melville, New York, USA), to prevent corneal drying. Deer were masked and weighed to the nearest 0.45 kg on a platform scale.

Twenty-one deer were assigned randomly to one of three α_2 antagonist treatments. Treatments were either 200 mg of tolazoline (100 mg/ml, Tolazine®; Lloyd Laboratories, Shenandoah, Iowa, USA), 11 mg of atipamezole (5 mg/ml, Antisedan®; Pfizer Animal Health, Exton, Pennsylvania, USA), or 15 mg of yohimbine (5 mg/ml, Antagonil®; Wildlife Pharmaceuticals), injected half intravenously (IV) and half subcutaneously, 45 min after the TZ/X injection. To facilitate a metered IV delivery of antagonists, sterile saline was added (when necessary) to syringes until total volumes reached 2 ml. All IV injections were delivered over 30 sec.

Ten additional immobilizations were conducted as described above, with deer being randomly assigned to one of two treatments. However, five deer were assigned to a control group, which received tolazoline as described above, plus a second IM injection of 3.6 ml 99% dimethyl sulfoxide (DMSO; The Butler Company, Columbus, Ohio, USA). Five deer were assigned to a group that received tolazoline as before, plus a second IM injection of 3.6 ml DMSO containing 5 mg of FLU (Sigma-Aldrich, St. Louis, Missouri, USA). The use of DMSO as a carrier was necessary because of the low solubility of FLU (Sigma-Aldrich).

The time until each deer raised its head or reached a standing position was recorded. Beginning 30 min after the antagonist injection, a sedation score was assigned to each deer at 30-min intervals for 5 hr. Scores were based on the following behavioral criteria and evaluated on a scale from 5 to 0: 5 = lateral recumbency with no sign of reversal; 4 = lateral recumbency, unable to maintain the head erect, and noticeable eye or ear movement; 3 = unable to stand, fairly dazed and unsteady, but able to hold head up; 2 = standing with moderate ataxia, braced stance, and sometimes lowered head; 1 = minimal sedation characterized by drooping eyelids; 0 = no sign of sedation. In addition, the times from antagonist injection to head raising (head-up) and standing were recorded.

Differences among the three antagonist treatments for time of head-up, time until standing, and sedation scores were determined by one-way analysis of variance for each 30 min time period and Duncan's multiple-range test (SAS Institute, Cary, North Carolina, USA). Treatment-related differences in time until head-up, time until standing, and sedation scores for the DMSO control group and the FLU/DMSO groups were determined with Student's *t*-test. Differences among treatments were evaluated at $P<0.05$.

RESULTS

Deer were satisfactorily immobilized on all 31 occasions with an IM injection of 220 mg of TZ (4.5±0.4 mg/kg) and 110 mg of X (2.2±0.2 mg/kg). Mean times (±SD)

TABLE 1. Mean time (min) until head up and standing in 21 captive white-tailed deer immobilized with tiletamine-zolazepam/xylazine (220 mg tiletamine-zolazepam [4.5 ± 0.4 mg/kg] and 110 mg of xylazine [2.2 ± 0.2 mg/kg]) and given one of three alpha$_2$ antagonists, October–November 2002, Athens, Georgia.

Alpha$_2$ antagonist	No.	Time (min) until head up (± SD)[a]	Time (min) until standing (± SD)[a]
Yohimbine (15 mg; 0.30 ± 0.02 mg/kg)	6[b]	62.3±42.7 A	112.0±56.4 A
Atipamezole (11 mg; 0.23 ± 0.02 mg/kg)	7	24.3±17.1 B	89.7±62.8 A
Tolazoline (200 mg; 4.0 ± 0.4 mg/kg)	7	21.3±14.3 B	52.6±37.2 A

[a] Means with the same letter in the same column are not statistically different.
[b] One deer that received yohimbine did not raise its head or stand within the 5 hr of monitoring.

from TZ/X injection to first effect, sternal recumbency, and lateral recumbency were 1.4±0.5, 2.4±0.7, and 3.0±0.9 min, respectively.

Mean times from antagonist injection until head-up were longer for deer that received yohimbine than deer treated with either atipamezole or tolazoline (Table 1). However, mean times from antagonist injection until standing were not different among yohimbine, atipamezole, or tolazoline (Table 1). Mean sedation scores for all three treatments decreased with time after the antagonist injection (Fig. 1). During the first 2 hr after the antagonist injection, mean sedation scores were higher for yohimbine than for atipamezole or tolazoline treatments. The mean sedation scores for atipamezole treatments were higher than those of tolazoline treatments in two of 10 observation periods (Fig. 1).

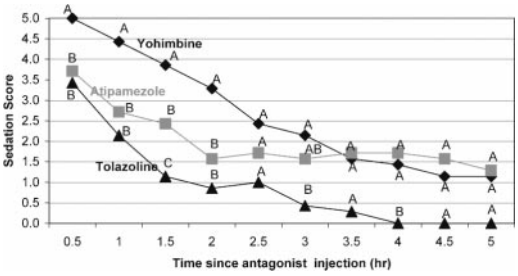

FIGURE 1. Mean sedation scores for 21 captive white-tailed deer immobilized with tiletamine-zolazepam/xylazine (220 mg tiletamine-zolazepam [4.5 ± 0.4 mg/kg] and 110 mg of xylazine [2.2 ± 0.2 mg/kg]) and given one of three α_2 antagonists, October to November 2002, Athens, Georgia. Antagonist treatments with the same letter at each time point are not significantly different. Sedation score of 5 = lateral recumbancy with no sign of reversal. Sedation score of 0 = no sign of sedation.

No treatment-related differences between the DMSO control group and the FLU/DMSO group were found for head-up times (19.8±13.1 and 24.6±13.8, respectively) or standing times (49.0±47.3 and 83.0±50.1, respectively). No treatment-related differences were detected for mean sedation scores in any of the observation periods between DMSO control and the FLU/DMSO groups.

DISCUSSION

Although, yohimbine, an α_2 antagonist has long been used for reversal of xylazine in white-tailed deer (Hsu and Shulaw, 1984; Mech et al., 1985) our results demonstrate that yohimbine does not antagonize the sedative effects of xylazine on deer as quickly or completely as atipamezole or tolazoline.

Atipamezole is more potent and selective for α_2 receptors than tolazoline or yohimbine (Jalanka and Roeken, 1990; Arnemo et al., 1993; Kreeger, 1996). Atipamezole is a specific α_2-antagonist that is primarily used for the reversal of medetomidine (a specific α_2 agonist). Ancrenaz (1994) reported that atipamezole was effective at reversing xylazine immobilization in captive Arabian oryx (*Oryx leucoryx*); however, there was a problem with resedation occurring 2–5 hr after atipamezole injection in many of the animals. Nicholls et al. (1996) reported that grey duikers (*Sylvicapra grimmia*) immobilized with K/X showed variable reversal of sedation

with atipamezole. Complete reversal of xylazine-induced immobilization by atipamezole has been reported in axis deer (*Axis axis*; Arnemo et al., 1993). However, on the basis of sedation scores, Arnemo et al. (1993) reported atipamezole performed comparably to tolazoline until 2–3 hr after antagonist injection. We also observed similar trends in sedation scores for atipamezole and tolazoline (Fig. 1).

Compared with atipamezole and yohimbine, tolazoline has the lowest affinity for all α_2-adrenergic receptor subtypes (Schwartz and Clark, 1998). Tolazoline has been effective in antagonizing xylazine in white-tailed deer (Kreeger et al., 1986; Dew, 1988; Del Giudice et al., 1989). Although sedation scores for tolazoline were only statistically lower than scores for atipamezole in two of 10 observation periods and were lower than yohimbine in six of 10 observation periods, we believe that tolazoline qualitatively outperformed yohimbine and atipamezole in the present study (Fig. 1).

Flumazenil is an antagonist with a great affinity for benzodiazepine receptors and rapidly reverses all actions of benzodiazepines, such as zolazepam, without adverse side effects (Klein and Klide, 1989). The recovery time of river otters (*Lutra canadensis*) immobilized with TZ was shortened with the use of FLU at a ratio of 1 mg FLU to 25 mg zolazepam (Spelman et al., 1997). Anesthesia of babirusa (*Babyrousa babyrussa*) immobilized with TZ/X was effectively reversed with the combination of yohimbine and FLU at a ratio of 1 mg FLU to 20 mg zolazepam (James et al., 1999). Walzer and Huber (2002) reported partial antagonism of TZ-treated cheetahs using FLU and another benzodiazepine antagonist, sarmazenil.

In the present study, the deer given FLU in a DMSO carrier at a ratio of 1 mg FLU to 22 mg zolazepam did not recover faster than the DMSO control deer. Walzer and Huber (2002) believed that the effects of benzodiazepine antagonists could not be predicted for different species immobilized with TZ. We did not find any reference for using FLU in cervids; however, the recovery of TZ/X-treated red deer (*Cervus elaphus hippelaphus*) was not hastened by the use of another benzodiazepine antagonist, samarzenil (Janovsky et al., 2000). It is possible that deer are not as responsive to benzodiazepine antagonists as other species. Additionally, FLU is only soluble at ≤1.5 mg/ml DMSO (Sigma-Aldrich). The extensive dilution of FLU may have reduced its efficacy. The cost for each antagonist was $5.63/deer for yohimbine, $18.92/deer for atipamezole, $2.56/deer for tolazoline, and $22.72/deer for FLU.

The reversal of TZ/X immobilization can be accomplished with any of the three α_2-antagonists tested. However, tolazoline reversed the effects of TZ/X more rapidly and more completely than either atipamezole or yohimbine, and tolazoline was the least expensive antagonist. The addition of FLU did not have any noticeable effects on recovery from TZ/X immobilization. On the basis of these results, we recommend the use of TZ/X for darting wild white-tailed deer and partial antagonism with tolazoline.

ACKNOWLEDGMENTS

This project was funded by the University of Tennessee, Hatch funding (TEN00228), and the University of Georgia McIntire-Stennis Project. Antler King Trophy Products, Inc., Moultrie Feeders, Inc., and Pennington Seed, Inc., made additional financial contributions. The authors gratefully acknowledge W. Lance of Wildlife Pharmaceuticals, Inc., for generous contributions of materials. We also are indebted to S. Dahmes for video recording immobilizations. We thank B. Chesser, S. Fischer, A. Goodman, M. Haun, and students from the University of Tennessee, Knoxville, for assistance with deer immobilizations.

LITERATURE CITED

ANCRENAZ, M. 1994. Use of atipamezole to reverse xylazine tranquilization in captive Arabian oryx (*Oryx leucoryx*). Journal of Wildlife Diseases 30: 592–595.

ARNEMO, J. M., S. R. MOE, AND N. E. SØLI. 1993. Xylazine-induced sedation in axis deer (*Axis axis*)

and its reversal by atipamezole. Veterinary Research Communications 17: 123–128.

DEL GIUDICE, G. D., P. R. KRAUSMAN, E. S. BELLANTONI, R. C. ETCHBERGER, AND U. S. SEAL. 1989. Reversal by tolazoline hydrochloride of xylazine hydrochloride-ketamine hydrochloride immobilizations in free-ranging desert mule deer. Journal of Wildlife Diseases 25: 347–352.

DEW, T. L. 1988. Use of tolazoline hydrochloride to reverse multiple anesthetic episodes induced with xylazine hydrochloride and ketamine hydrochloride in white-tailed deer and goats. Journal of Zoo Animal Medicine 19: 8–13.

HAIGH, J. C., I. STERLING, AND E. BROUGHTON. 1985. Immobilization of polar bears (*Ursus maritimus phipps*) with a mixture of tiletamine hydrochloride and zolazepam hydrochloride. Journal of Wildlife Diseases 21: 43–47.

HSU, W. H., AND W. P. SHULAW. 1984. Effect of yohimbine on xylazine-induced immobilization in white-tailed deer. Journal of the American Veterinary Medical Association 185: 1301–1303.

JALANKA, H. H., AND B. O. ROEKEN. 1990. The use of medetomidine, medetomidine-ketamine combinations, and atipamezole in nondomestic mammals: A review. Journal of Zoo and Wildlife Medicine 21: 259–282.

JAMES, S. B., R. A. COOK, B. L. RAPHAEL, M. D. STETTER, P. KALK, K. MACLAUGHLIN, AND P. P. CALLE. 1999. Immobilization of babirusa (*Babyrousa babyrussa*) with xylazine and tiletamine/zolazepam and reversal with yohimbine and flumazenil. Journal of Zoo and Wildlife Medicine 30: 521–525.

JANOVSKY, M., F. TATARUCH, M. AMBUEHL, AND M. GIACOMETTI. 2000. A Zoletil®-Rompun® mixture as an alternative to the use of opioids for immobilization of feral red deer. Journal of Wildlife Diseases 36: 663–669.

KILPATRICK, H. J., AND S. M. SPOHR. 1999. Telazol®-xylazine versus ketamine-xylazine: A field evaluation for immobilizing white-tailed deer. Wildlife Society Bulletin 27: 566–570.

KLEIN, L. V., AND A. M. KLIDE. 1989. Central α_2 adrenergic and benzodiazepine agonists and their antagonists. Journal of Zoo and Wildlife Medicine 20: 138–153.

KREEGER, T. J. 1996. Handbook of wildlife chemical immobilization. Wildlife Pharmaceuticals, Laramie, Wyoming, 340 pp.

———, G. D. DEL GIUDICE, U. S. SEAL, AND P. D. KARNS. 1986. Immobilization of white-tailed deer with xylazine hydrochloride and ketamine hydrochloride and antagonism by tolazoline hydrochloride. Journal of Wildlife Diseases 22: 407–412.

MECH, L. D., G. D. DEL GIUDICE, P. D. KARNS, AND U. S. SEAL. 1985. Yohimbine hydrochloride as an antagonist to xylazine hydrochloride-ketamine hydrochloride immobilization of white-tailed deer. Journal of Wildlife Diseases 21: 405–410.

MILLER, B. F., L. I. MULLER, T. N. STORMS, E. C. RAMSAY, D. A. OSBORN, R. J. WARREN, K. V. MILLER, AND K. A. ADAMS. 2003. A comparison of carfentanil/xylazine and Telazol®/xylazine for immobilization of white-tailed deer. Journal of Wildlife Diseases 39: 851–858.

MILLSPAUGH, J. J., G. C. BRUNDIGE, J. A. JENKS, C. L. TYNER, AND D. R. HUSTEAD. 1995. Immobilization of Rocky Mountain elk with Telazol® and xylazine hydrochloride, and antagonism by yohimbine hydrochloride. Journal of Wildlife Diseases 31: 259–262.

MURRAY, S., S. L. MONFORT, L. WARE, W. J. MCSHEA, AND M. BUSH. 2000. Anesthesia in female white-tailed deer using Telazol® and xylazine. Journal of Wildlife Diseases 36: 670–675.

NICHOLLS, P. K., T. A. BAILEY, C. A. BAKER, AND K. WILSON. 1996. Anesthesia of the grey duiker (*Sylvicapra grimmia*) using a combination of ketamine and xylazine, with reversal by atipamezole. Journal of Zoo and Wildlife Medicine 27: 49–53.

NIELSEN, L. 1999. Chemical immobilization of wild and exotic animals. Iowa State University Press, Ames, Iowa, 341 pp.

SCHWARTZ, D. D., AND T. P. CLARK. 1998. Selectivity of atipamezole, yohimbine and tolazoline for α_2-adrenergic receptor subtypes: Implications for clinical reversal of α_2-adrenergic receptor mediated sedation in sheep. Journal of Veterinary Pharmacology and Therapeutics 21: 342–347.

SPELMAN, L. H., P. W. SUMNER, W. B. KARESH, AND M. K. STOSKOPF. 1997. Tiletamine-zolazepam anesthesia in North American river otters (*Lutra canadensis*) and its partial antagonism with flumazenil. Journal of Zoo and Wildlife Medicine 28: 418–423.

WALZER, C., AND C. HUBER. 2002. Partial antagonism of tiletamine-zolazepam in cheetah. Journal of Wildlife Diseases 38: 468–472.

Received for publication 16 July 2003.