Partial Antagonism of Tiletamine-Zolazepam Anesthesia in Cheetah

Authors: Walzer, C., and Huber, C.

Source: Journal of Wildlife Diseases, 38(2) : 468-472

Published By: Wildlife Disease Association

URL: https://doi.org/10.7589/0090-3558-38.2.468

Journal of Wildlife Diseases, 38(2), 2002, pp. 468–472

Partial Antagonism of Tiletamine-Zolazepam Anesthesia in Cheetah

C. Walzer,[1,2] **and C. Huber**[1] [1] Salzburg Zoo Hellbrunn, A-5081 Anif, Austria; [2] Corresponding author (email: chwalzer@eunet.at).

ABSTRACT: This study evaluated partial antagonism of tiletamine-zolazepam (TZ) anesthesia in cheetahs (*Acinonyx jubatus*) and differences between two benzodiazepine antagonists, flumazenil and sarmazenil, in this species. Four cheetahs were anesthetized three times at an interval of 14 days with an average intramuscular dose of 4.2 mg/kg TZ. In trials 2 and 3 flumazenil at 0.031 mg/kg and sarmazenil at 0.1 mg/kg, respectively, were applied intramuscularly 30 min after initial TZ injection. There was a highly significant difference between the duration of TZ anesthesia with and without antagonist. Use of the antagonists significantly shortened duration and recovery and eliminated excitatory behavior during the recovery phase. No significant differences could be determined between the two antagonists. We recommend the use of sarmazenil and flumazenil to antagonize TZ anesthesia in cheetahs.

Key words: *Acinonyx jubatus*, anesthesia, antagonist, cheetah, flumazenil, sarmazenil, tiletamine-zolazepam.

The largest remaining free-ranging population of cheetahs (*Acinonyx jubatus*) survives predominantly on farmland in Namibia (Nowell and Jackson, 1996). Livestock predation and subsequent anti-predator actions from local farmers are a limiting factor in this population. Various nongovernmental organizations in Namibia attempt to rehabilitate cheetahs captured by farmers. During these activities the animals are routinely immobilized with a combination of tiletamine hydrochloride and zolazepam hydrochloride (TZ). The primary aim of this study was to evaluate partial antagonism of TZ anesthesia in the field and to test for possible differences between two benzodiazepine antagonists.

Tiletamine hydrochloride is a dissociative anesthetic, pharmacologically similar to ketamine hydrochloride (Lin et al., 1993). Tiletamine is three to four times more potent than ketamine (Swan, 1993). Zolazepam is a diazepinone minor tranquillizer similar to diazepam. Use of tiletamine alone can cause convulsions, therefore, it is combined with the anti-convulsive zolazepam. Tiletamine-zolazepam combinations are regularly used in veterinary medicine to anesthetize many species (Hugues et al., 1986; Schobert, 1987; Walzer, 1995) including captive and free-ranging cheetahs (Hugues et al., 1986; McKenzie and Burroughs, 1993). In Europe TZ is available in a 1:1 combination of 100 and 500 mg (Zoletil® 50 and 100, Virbac SA, Louvain la Neuve, Belgium).

Flumazenil (Anexate® Roche, Hoffmann-LaRoche Basel, Switzerland) and sarmazenil (Sarmasol®, Dr. E. Graeub AG, Bern, Switzerland) are both competitive benzodiazepine receptor blockers in the central nervous system. Flumazenil is a 1,4-imidazobenzodiazepine derivate and was developed as a specific antagonist for therapeutic doses or overdoses of benzodiazepines in humans. Diazepam and midazolam-induced sedation, respiratory depression, and muscle relaxation in humans can be reversed by flumazenil (Lauven et al., 1985; Klein and Kilde, 1989; Gross et al., 1991). Flumazenil also has been used in veterinary anesthesia: dogs (Hess, 1991), cats (Lin et al., 1993), river otters (*Lutra canadensis*) (Spelman, 1997), and guanacos (*Lama guanicoe*) (Karesh et al., 1998). The benzodiazepine receptor partial inverse agonist sarmazenil has been used as an antagonist for climazolam in horses (Bettschart-Wolfensberger et al., 1996), guinea-pigs (Henke et al., 1996), and dogs (Henke et al., 1991) and for diazepam in elephant seals (*Mirounga leonina*) (Woods et al., 1995) and squirrel monkeys (*Saimiri sciureus*) (Martin et al., 1998). Furthermore sarmazenil is under investigation for the treatment of hepatic encephalopathy in the dog (Meyer and Rothuizen, 1998).

This study was conducted at the veterinary medical facility at the Salzburg Zoo, Austria (47°35′N, 13°02′E, 460 m elevation). All cheetahs were held in similar holding pens (100 m^2 under standard conditions throughout the trial period. The trial was carried out in accordance with Austrian animal welfare legislation (Permit No. 9/01-40.034/81-1998).

Four captive cheetahs (two yearling males and two yearling females) were anesthetized three times each at an interval of 14 days with an average intramuscular dose of 4.2 ± 0.2 mg/kg body weight (BW) TZ applied by blow dart into the rear leg muscles. In the first trial no antagonist was applied. Based on previous clinical experience, in trials 2 and 3, respectively, flumazenil at 0.031 ± 0.006 mg/kg and sarmazenil at 0.1 mg/kg were injected intramuscularly by hand 30 min after initial TZ application. Thirty minutes was estimated to be a realistic handling time for field work. Anesthesia was monitored using sequential rectal temperature measurements, thoracic excursion and auscultation, heart rate, and relative percent oxyhemoglobin saturation measured with a pulse oximeter (Nellcor NP-20, Nellcor Incorporated, Pleasanton, California, USA). Pain perception was evaluated by pinching the skin between the toes with a hemostat and recording a withdrawal reflex. Myorelaxation was evaluated subjectively by flexing the hind limb.

The following intervals were measured in relation to time after injection of the antagonist (t-antag) and time after injection of the initial TZ (t-total); initial ataxia and sedation, lateral recumbency, first sign of recovery-head held up (HU), first attempt to rise (SUA), successful rise and walking (SUS). After successful walking was noted, the animals were observed for a further 6 hr in order to evaluate possible resedation.

Interval scan sampling was used to record behavioral data during anesthesia. Observation times were divided into sample intervals of 60 sec (Martin and Bateson, 1993). Time intervals were measured using a stopwatch (PC 80A Professional Stopwatch, Conrad Electronics GmbH, Hirschau, Germany). Because data were not normally distributed, the results were evaluated and compared using the Mann-Whitney *U*-test. Statistical significance was determined at $P < 0.05$.

Induction of anesthesia was rapid and calm in all trials. With TZ, initial effects occurred within 2.9 ± 0.8 min and lateral recumbency was achieved within 5.8 ± 3 min in all 12 procedures. No significant difference between the various TZ induction periods was found (Mann-Whitney *U*-test, $P > 0.05$). Myorelaxation was considered generally good. A slow and retracted limb withdrawal reflex was elucidated in all procedures. The physiologic parameters monitored did not differ significantly between the examined cheetahs or procedures.

In the TZ trial without a partial antagonist, duration and recovery from anesthesia was individually variable. The first recovery phase (ca. 35 min) was considered to be rough; the animals would throw their heads around in a jerking motion repeatedly hitting the floor. When flumazenil and sarmazenil were used as partial antagonists the duration and recovery from anesthesia was significantly shortened ($P > 0.05$). In contrast to the recovery period without the use of antagonists, recovery with antagonist was calm and smooth. Results are presented in Table 1. Resedation was not noted in any of the trials.

There was no significant difference between the two antagonists in any of the defined time intervals ($P > 0.05$). Highly significant differences were found between duration and recovery phases with and without antagonist ($P < 0.05$). Though not significant, when sarmazenil was used initial recovery was slightly shorter.

Induction of anesthesia with TZ was calm and rapid in all cheetahs. This was similar to induction periods recorded in other species with this combination (Walzer, 1995; Spelman et al., 1997). This dem-

TABLE 1. Comparison of tiletamine-zolazepam (TZ), TZ–flumazenil, and TZ–sarmazenil anesthesia[a] in four cheetahs.

	Init. eff.	Lat. rec.	HU (t-antag)	HU (t-total)	SUA (t-antag)	SUA (t-total)	SUS (t-antag)	SUS (t-total)
TZ								
Mean	3.3	7.3	NA	71.3	NA	140	NA	207.5
SD	1.1	4.5	NA	28.4	NA	12.2	NA	35.6
TZ+Flumazenil								
Mean	2.5	5.3	5	37	40.3	74.8	66.8	98.8
SD	0.5	1.3	1.9	3.5	22.3	16.7	15.2	5.6
TZ+Sarmazenil								
Mean	3	4.75	5.25	36.5	17	48.3	64.3	95.5
SD	0.7	1.9	1.5	6.5	8.5	13.9	32.9	37.6

[a] Init. eff. = initial effect, Lat. rec. = lateral recumbency, HU = head up, SUA = stand up attempt, SUS = stand up and walk successfully, t-antag = time since injection of the antagonist, t-total = total time since TZ injection, NA = not applicable. Times are in minutes.

onstrates the usefulness of this drug combination when dealing with an emergency such as an escaped animal in a zoo setting. Recovery from anesthesia was prolonged (207 ± 35 min t-total) and considered rough when an antagonist was not used. Rough recoveries have been noted previously in various species (Millspaugh et al., 1995; Walzer, 1995; Lin, 1996). A significant shortening of the recovery period was obtained when either flumazenil or sarmazenil was used. Furthermore the recovery was markedly calmer when the partial antagonists were used. A slow and retracted limb withdrawal reflex was elucidated in all procedures. Analgesia was therefore deemed to be adequate for minor procedures only. No significant difference was detected between the two-benzodiazepine antagonists. Resedation was not noted in the 6 hr following successful walking in any of the trials.

The average dose used for the flumazenil (0.031 ± 0.006 mg/kg) in this study is 2.5 times lower than the dose used in river otters (Spelman, 1997) and three times lower than the dose used in guanacos (Karesh et al., 1998). Similar to Spelman et al. (1997) we found a significant shortening of the recovery phase following the application of an antagonist. However, a shortening of the recovery period following flumazenil application was not apparent in guanacos (Karesh et al., 1998). As in European brown bear (*Ursus arctos*) (Walzer, 1997) a marked increase in depth of respiration following flumazenil injection was noted in guanacos.

As in other studies we recorded a significant reduction in anesthetic recovery time when using sarmazenil. Similar to flumazenil, successful walking was possible after 96 min. The average dose of sarmazenil used in this study was 0.1 mg/kg. This is 2.5 times higher than the dose used in domestic ponies to antagonize climazolam (Bettschart-Wolfensberger et al., 1996) and three times higher than the dose used in red deer (*Cervus elaphus*) (Janovsky et al., 2000) but three times lower than the dose used in guinea pigs (Henke et al., 1996) and 10 times lower than the dose used in elephant seals (Woods et al., 1995). Directly comparing these reports is difficult because various benzodiazepines were antagonized and in other protocols a combination of several antagonists (naloxone, sarmazenil, and yohimbine) was used. Only one report of use of sarmazenil to antagonize zolazepam in a TZ-xylazine mixture was found. The addition of sarmazenil to the second antagonist, yohimbine hydrochloride, did not significantly reduce recovery time compared to use of

yohimbine alone in red deer (Janovsky et al., 2000).

When using partial antagonists care must be taken to avoid adverse excitatory effects from other components, such as tiletamine, in the anesthetic combination. If the pharmacodynamics of TZ are known in a species the effect of partial antagonism can be anticipated. When flumazenil was evaluated in the domestic cat and the dog both species recovered more rapidly than from TZ anesthesia alone; however, dogs demonstrated excitatory behavior during the recovery phase (Bednarski et al., 1989; Lin et al., 1993). In contrast to dogs, and similar to domestic cats and river otters, cheetahs appear to metabolize the tiletamine rapidly, avoiding excitatory behavior after antagonism of the protective zolazepam. This study shows that the zolazepam antagonists, flumazenil and sarmazenil, can be used to safely reduce recovery time from TZ anesthesia in cheetahs.

Administration of flumazenil or sarmazenil is recommended 30 min after application of TZ in the cheetah. Not only is the recovery period significantly shortened, but also recovery is markedly calmer. An important additional factor to consider is the cost of the antagonists, which in large animals can be considerable. In the dose used in this study flumazenil is five times more expensive than sarmazenil. We agree with Spelman et al. (1997) in advocating caution when using benzodiazepine antagonists in conjunction with TZ anesthesia in a new species because the effect cannot be predicted.

The authors wish to thank L. Slotta Bachmayr for help with the statistics and the animal keepers and J. Angermann and B. Kameri for their support and help during this project.

LITERATURE CITED

BEDNARSKI, R. M., W. M. MUIR, AND C. H. TRACY. 1989. The effects of tolazoline, doxapram and RO15-1788 on the depressant action of Telazol®. Veterinary Medicine 84: 1016–1022.

BETTSCHART-WOLFENSBERGER, R. P., M. TAYLOR, AND J. W. SEAR. 1996. Physiological effects of anesthesia induced and maintained by intravenous administration of a climazolam-ketamine combination in ponies premedicated with acepromazine and xylazine. American Journal of Veterinary Research 57: 1472–1477.

GROSS, J. B., R. S. WELLER, AND P. CONRAD. 1991. Flumazenil antagonism of midazolam-induced ventilatory depression. Anesthesiology 75: 179–185.

HENKE, J., C. MOLL, S. WINKLER, B. GUSSREGEN, H. BOCKELUHR, L. RUPRECHT, M. NUSSL, AND W. ERHARDT. 1991. Comparative investigations on ultrashort anesthetic methods in dogs. Journal of Veterinary Anesthesia, special supplement, Proceedings of the 4th International Congress of Veterinary Anesthesia, Utrecht, Netherlands, pp. 25–31.

———, U. ROBERTS, K. OTTO, C. LENDL, U. MATIS, T. BRILL, AND W. ERHARDT. 1996. Klinische Untersuchungen zur i.m. Kombinationsanaesthesie mit Fentanyl/Climazolam/Xylazin und postoperative i.v. Anatgonisierung mit Naloxon/Sarmazenil/Yohimbin beim Meerschweinchen. Tierarztliche Praxis 24: 85–87.

HESS, L. 1991. Anästhesie beim Hund mit dem Kombinationspraparat Tilest 500. Tierarztliche Praxis 19: 107–110.

HUGUES, F., M. LECLERC-CASSAN, AND J. P. MARC. 1986. Anesthésie des animaux non-domestiques. Essai d'un nouvel anesthésique: l'association Tiletamine-Zolazepam (Zoletil N.D.) Records Medical Veterinaires 162: 427–431.

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.

KARESH, W. B., M. M. UHART, E. S. DIERENFELD, W. E. BRASELTON, A. TORRES, C. HOUSE, H. PUCHE, AND R. A. COOK. 1998. Health evaluation in free-ranging guanaco (*Lama guanicoe*). Journal Zoo and Wildlife Medicine 29: 134–141.

KLEIN, L. V., AND A. M. KILDE. 1989. Central alpha-2 adrenergic and benzodiazepine agonists and their antagonists. Journal Zoo and Wildlife Medicine 20: 138–153.

LAUVEN, P. M., H. SCHWILDEN, AND H. H. STOECKEL. 1985. The effects of a benzodiazepine antagonist RO15-1788 in the presence of stable concentrations of midazolam. Anesthesiology 63: 61–64.

LIN, H. C. 1996. Dissociative anesthetics. *In* Lumb and Jones' veterinary anesthesia, J. C. Thurman, W. J. Tranquilli and G. J. Benson (eds.). Williams and Wilkins, Media, Pennsylvania, pp. 241–296.

———, J. C. THURMON, G. J. BENSON, AND W. J. TRANQUILLI. 1993. Telazol—A review of its pharmacology and use in veterinary medicine.

Journal Veterinary Pharmacology and Therapy 16: 383–418.

MARTIN, P., AND P. BATESON. 1993. Measuring behaviour; An introductory guide. Cambridge University Press, Cambridge, UK, pp. 84–98.

———, J. L. MOREAU, F. JENCK, AND L. PIERI. 1998. Sarmazenil precipitated withdrawal: A reliable method for assessing dependence liability of benzodiazepine receptor ligands. Pharmacology Biochemistry and Behaviour 59: 939–944.

MCKENZIE, A., AND R. BURROUGHS. 1993. Chemical capture of carnivores. *In* Capture and care manual, A. McKenzie (ed.). Wildlife Decision Services, Pretoria, South Africa, pp. 224–244.

MEYER, H. P., AND J. ROTHUIZEN. 1998. Modulation of the GABAergic tone by benzodiazepines receptor ligands in chronic hepatic encephalopathy in the dog. Vet-Q 20 Supp l: S100-1.

MILLSPAUGH, J. L., 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.

NOWELL, K., AND P. JACKSON. 1996. Sub-Saharan Africa. Status survey and conservation action plan—wild cats. International Union for the Conservation of Nature, Gland, Switzerland, pp. 12–17.

PLUM, D. C. 1999. Veterinary drug handbook, 3rd Edition. Iowa State University Press, Ames, Iowa, pp. 62–63.

SCHOBERT, E. 1987. Telazol® use in wild and exotic animals. Veterinary Medicine 82: 1080–1088.

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

SWAN, G. E. 1993. Drugs used for the immobilization, capture, and translocation of wild animals. *In* Capture and care manual, A. McKenzie (ed.). Wildlife Decision Services, Pretoria, South Africa, pp. 2–64.

WALZER, C. 1995. Beitrag zur Immobilisation von Wildschweinen mit Tiletamine-Zolazepam. Wiener Tierärztliche Monatschrift 82: 29–31.

———. 1997. Beitrag zur Braunbär—Narkose und Fang im Zoo und in der freien Wildbahn. Tagungsbericht 17 Arbeitstagung der Zootierärzte im deutschsprachigen Raum, pp. 29–31.

WOODS, R., S. MCCLEAN, S. NICOL, AND H. BURTON. 1995. Antagonism of some cyclohexamide-based drug combinations used for chemical restraint of southern elephant seals (*Mirounga leonina*). Australian Veterinary Journal 72: 165–171.

Received for publication 27 December 2000.