

YOHIMBINE AS AN ANTAGONIST TO KETAMINE-XYLAZINE IMMOBILIZATION IN BLACK BEARS

DAVID L. GARSHELIS, Forest Wildlife Populations and Research Group, Minnesota Department of Natural Resources, 1201 East Highway 2, Grand Rapids, MN 55744

KAREN V. NOYCE, Forest Wildlife Populations and Research Group, Minnesota Department of Natural Resources, 1201 East Highway 2, Grand Rapids, MN 55744

PATRICK D. KARNS, Forest Wildlife Populations and Research Group, Minnesota Department of Natural Resources, 1201 East Highway 2, Grand Rapids, MN 55744

Abstract: During May-July, 1981-85, 111 black bears (*Ursus americanus*) were immobilized with ketamine (\bar{x} = 5.0 mg/kg) and xylazine (\bar{x} = 2.0 mg/kg). Time from complete immobilization to recovery (walking) ranged from 22 to 140 min. We experimented with yohimbine (0.04-0.35 mg/kg) to counteract immobilization and thereby speed recovery. Eleven bears were given intramuscular injections of yohimbine, of which only 2 (18%) recovered within 10 min. In contrast, 35 bears were given intravenous injections of yohimbine, of which 31 (89%) recovered within 10 min (median = 5 min). Heart rates increased an average of 61% within 1 min of intravenous injections. Two bears that were immobilized with ketamine alone (10 mg/kg and 17 mg/kg) did not recover within 10 min after intravenous injection of yohimbine, although their heart rates increased appreciably. These data suggest that yohimbine antagonizes the effects of xylazine but likely does not counteract the effects of ketamine. We tested 3 dosages of yohimbine with respect to the dosage of xylazine (0.05, 0.10, and 0.15 mg yohimbine/mg xylazine) and found no differences in recovery times. Also, no relationships were observed between recovery times after yohimbine injection and the weight, age, or sex of the bear, dose of yohimbine given, time since immobilization (range 10-66 min), or the dose of ketamine given (range 2.7-8.9 mg/kg). We conclude that an intravenous injection of 0.05 mg yohimbine/mg xylazine provides a safe and effective antagonist to ketamine-xylazine immobilization in black bears.

Int. Conf. Bear Res. and Manage. 7:323-327

Field research studies of bears rely heavily on safe and effective immobilizing drugs. Beginning in the late 1960s, 2 classes of drugs became widely used to restrain bears: narcotics and cyclohexamines. The narcotic etorphine hydrochloride (M99, American Cyanamid) gained popularity because its effects can be readily reversed using diprenorphine (M50-50), cyprenorphine (M285), or naloxone (Narcan) (Bee-man et al. 1974, Miller and Will 1976). However, etorphine is expensive, and procurement requires a special license. Also, extremely small doses can kill humans and have killed bears injected during hibernation (M. R. Pelton, pers. commun.).

Cyclohexamines are less expensive and generally easier to obtain and safer to handle than narcotics. Three different cyclohexamines have been used to immobilize bears. Phencyclidine hydrochloride (Sernylan, Parke-Davis) was popularly used until about 1980, when legal manufacture was discontinued in North America because of human abuse of it. Ketamine hydrochloride (Ketaset, Bristol Vet. Prod.) replaced phencyclidine as the drug of choice for many bear studies. Tiletamine hydrochloride has gained attention more recently but is not yet commercially available.

Cyclohexamines typically are mixed with a muscle relaxant to make bears less rigid during handling and to reduce the incidence of convulsions. Tiletamine mixed 1:1 with the tranquilizer zolazepam hydrochloride (marketed as Telazol or CI-744, Warner Lambert) has proven effective in both black bear and polar bear (*U. maritimus*) studies (Stewart et al. 1980,

Haigh et al. 1985, Stirling et al. 1985). Ketamine usually is combined with xylazine hydrochloride (Rompun, Haver-Lockhart) in a 1:1 or 2:1 mixture (Addison and Kolenosky 1979, Lee et al. 1981, Lynch et al. 1982). This mixture provides safe and relatively rapid (usually < 10 min) immobilization. One drawback in the use of ketamine-xylazine, however, has been the absence of a drug capable of reversing the immobilization.

Yohimbine hydrochloride, an alkaloid derived from several botanical sources, has been known for over 100 years (Goldberg and Robertson 1983). Historically it has been promoted as an aphrodisiac and may indeed enhance sexual motivation in males of some species (Clark et al. 1984). Recently, however, several studies have indicated that yohimbine also acts as an antagonist to ketamine or xylazine immobilization in various ungulates and carnivores (Hatch and Ruch 1974; Hatch et al. 1982, 1983; Hsu 1983; Jessup et al. 1983; Schmidt 1983; Hsu and Shulaw 1984; Mech et al. 1985; Ramsay et al. 1985; Renecker and Olsen 1986). During 1984 and 1985 we conducted a study to test whether yohimbine can be used to reverse ketamine-xylazine immobilization in black bears.

We thank K. D. Kerr for preparing the yohimbine solution and for suggesting dosage rates. P. L. Coy and D. L. Mayberry assisted with the capture and handling of bears. J. A. Summers typed the manuscript, and R. E. Lake, M. A. Ramsay, and U. S. Seal provided helpful criticisms. This study was funded by the Minn. Dep. of Nat. Resour.

METHODS

During May–July, 1981–85, black bears in north-central Minnesota were captured in barrel traps or Aldrich foot snares as part of a telemetry study on ecology and population dynamics. From 1981 to 1983 bears were immobilized with an intramuscular (IM) injection of ketamine (\bar{x} = 14.5 mg/kg, range 5.1–24.2 mg/kg, N = 73), whereas in 1984–85 and part of 1981 we used a 5:2 mixture of ketamine (\bar{x} = 5.0 mg/kg, range 2.7–8.9 mg/kg, N = 111) and xylazine (\bar{x} = 2.0 mg/kg). Immobilized bears were weighed on a spring scale, measured, ear-tagged, radio-collared, and tattooed. A 1st premolar was extracted for age estimation, and blood was drawn from a femoral vein.

The handling procedure usually required about 30 min but varied from 10 min to > 1 hour. Bears that began to recover before handling was completed were given additional shots of ketamine or ketamine-xylazine (whichever they were immobilized with initially). This often prolonged recovery well beyond the time necessary for processing. After processing, we waited 20–30 min to observe recovery. If bears did not leave the trapsite within that time, we left and returned later the same day to confirm that they had eventually recovered.

During 1984 and 1985 we experimented with yohimbine injection as a means of accelerating recovery from ketamine-xylazine immobilization. Yohimbine was constituted at 1.0 or 2.0 mg/ml of physiological (0.85%) saline. We administered yohimbine intravenously (IV) in a femoral vein (35 bears) or IM (11 bears) immediately after the handling procedure was completed, 10–66 min after the bear 1st became immobile. To ensure independence of samples, bears were given yohimbine only once a year, even though some individuals were captured and immobilized up to 3 times per year.

We suspected that yohimbine counteracted mainly the effects of xylazine (Hsu 1981, Goldberg and Robertson 1983), so dosages of yohimbine were chosen relative to the dose of xylazine. One of 3 dosages (0.05, 0.10, or 0.15 mg yohimbine/mg xylazine) was randomly selected for each bear before the handling procedure. The resultant dosage of yohimbine relative to body weight ranged from 0.04 to 0.35 mg/kg.

To test whether yohimbine antagonized the effects of ketamine, 2 bears were given IV injections of yohimbine (0.17 mg/kg and 0.42 mg/kg) following immobilization with straight ketamine (17 mg/kg and 10 mg/kg, respectively).

We measured pulse and respiration rates of immobilized bears just before and again 1 min after injecting yohimbine. After injecting yohimbine, we stood at least 3 m from the bear and quietly watched and timed its recovery. We recorded the time when it 1st began moving, when it lifted its head, and when it 1st began to move away. We made a subjective assessment of its coordination as it moved away.

RESULTS

Bears given yohimbine IV were immobilized for about the same total time (median = 40 min, range 15–73 min) as bears not given yohimbine and observed until recovery (median = 38 min, range 22–140 min, N = 41); however, the responses of bears to IV injections of yohimbine indicated that this drug did accelerate their recovery. Within 1 min of the IV injections of yohimbine, heart rates increased an average of 61% (range 0–133%) from a mean heart rate of 52 beats per minute (bpm) before yohimbine to 80 bpm after yohimbine. No consistent changes in respiration rate were observed. The 1st external signs of recovery were twitching and swatting mosquitos on the muzzle with a forepaw, followed by attempts to raise the head. Half of the 35 bears given yohimbine IV raised their heads within 3 min after yohimbine injection, and all but 1 did so within 10 min (range 1.0–13.0 min). Thirty-one (89%) of the bears given IV injections of yohimbine left the trapsite within 10 min of the injection (Fig. 1).

Bears given IM injections of yohimbine did not show the same responses as those given IV injections. We detected no change in heart rates of these bears within 1 min of yohimbine injection. Only 5 of 10 bears raised their heads within 10 min of IM injection (median = 11.0 min, range 3.0 to >20.0 min). This was significantly later than those given an IV injection (Mann-Whitney U = 292, P < 0.0003). Only 2 bears (18%) given yohimbine IM left the trapsite within 10 min, and only half left within 15 min (Fig. 1). This also was significantly later than those given yohimbine IV (Mann-Whitney U = 340, P < 0.0001).

Bears that recovered relatively rapidly after an injection of yohimbine often ran away (44% of those that left within 5 min of an IV yohimbine injection), whereas those that recovered more slowly (> 5 min) walked (94%). Human noises (e.g., hand clapping or vocalizations) generally prompted those that were walking to run. Bears usually were unsteady and intermittently lay down or fell down as they moved away, but they did not relapse into unconsciousness.

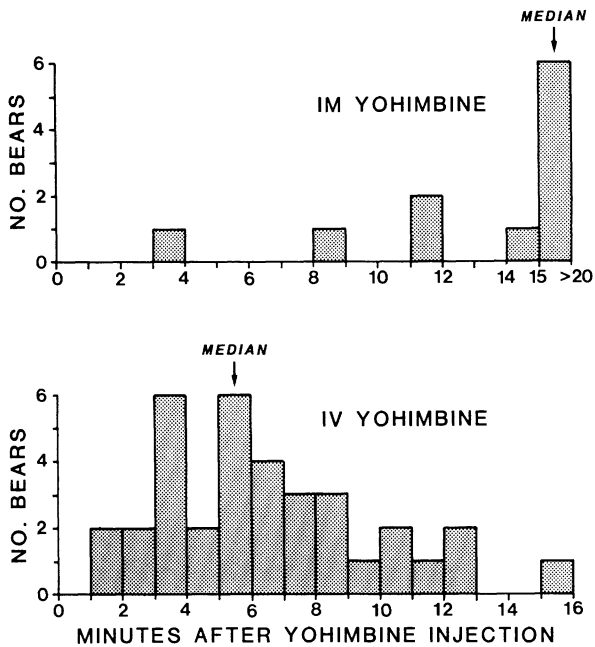


Fig. 1. Time until mobility after IM and IV injections of yohimbine in black bears immobilized with ketamine and xylazine.

No relationships were observed between the recovery times after IV yohimbine injections and the weight, age, or sex of the bear, the dose (mg or mg/kg) of yohimbine given, the time since immobilization, or the dose of ketamine-xylazine given. We also found no differences among recovery times related to the ratio of yohimbine/xylazine.

Neither of the bears immobilized with ketamine alone recovered within 10 min after an IV injection of yohimbine. Both exhibited increased heart rates and increased but shallower breathing. One crawled away slowly after 11 min (it could not be prompted to stand), whereas the other (given the higher dose of yohimbine) remained at the trapsite, standing and trembling, for at least 30 min.

DISCUSSION

The total time for recovery from ketamine-xylazine immobilization was similar for bears given yohimbine and those that were not. However, this comparison does not indicate the absence of an effect from yohimbine because unfortunately our observations of recovery times for bears not given yohimbine were biased against animals that took relatively long to recover. This bias arose because (1) bears that recovered immediately after processing was complete

were not given yohimbine, whereas in 1984–85 yohimbine was given to all bears that took longer to recover and (2) before we had yohimbine, bears that did not recover shortly after processing were not observed until recovery, so these ($N = 24$) relatively long recovery times could not be included in our analysis. We believe that the similarity of recovery times for bears that recovered quickly without yohimbine and those that did not recover quickly on their own but were given yohimbine IV indicates that the yohimbine did speed recovery. Our finding that 89% of bears given yohimbine IV left the trapsite within 10 min certainly documents the utility of this drug for arousing immobilized bears. There was no evidence in this study that IM injections of yohimbine hastened recovery.

Rapid reversal of immobilization is important in 2 respects. First, it saves time for researchers. Before using yohimbine, we waited up to 30 min after handling was completed for a bear to recover or we left the trapsite and returned several hours later to check that the animal had recovered. With yohimbine, the bear usually recovered and left the site before we finished packing up our trapping materials. Second, reversal of the immobilization is better for the bear. Although most bears appeared somewhat disoriented after they were given yohimbine, they were easily capable of running when prompted by human disturbance. Thus, the antagonism of ketamine-xylazine immobilization with yohimbine likely would enable a bear to more easily avoid drug-induced accidents and escape predators, such as other bears or wolves (*Canis lupus*). Yohimbine also would enable a bear to return to its normal activities (e.g., foraging, mating) or to its family group more readily than an animal left to recover without this antagonist.

Our tests with yohimbine on 2 bears immobilized with ketamine alone, although not conclusive, suggest that yohimbine counteracts mainly the effects of xylazine but not ketamine. Xylazine is believed to act as an agonist on the α_2 -adrenoreceptors (Berthelsen and Pettinger 1977). These receptors, located primarily at presynaptic sites on sympathetic neurons, inhibit norepinephrine release when stimulated by xylazine, resulting in muscle relaxation. Yohimbine binds selectively to α_2 -adrenoreceptors, possibly displacing xylazine, and thereby enabling normal release of norepinephrine and regained muscle control (Hoffman and Lefkowitz 1980, Goldberg and Robertson 1983). Immobilization of black bears with ketamine and xylazine requires less than half the amount of

ketamine than immobilization with ketamine alone (Hugie et al. 1976 and this study); therefore, when the effects of the xylazine are blocked by yohimbine, the remaining low dose of ketamine is not enough to maintain the immobilization and the animal becomes mobile, although still somewhat disoriented. Other α -adrenergic blocking agents (e.g., piperoxan, phenolamine, tolazoline) also reverse the action of xylazine, but their specificity for the α_2 site is not as great as that of yohimbine (Hoffman and Lefkowitz 1980, Hsu 1981), so they would likely not be as effective and could cause other side effects.

Yohimbine may have an additional benefit as a therapeutic drug for bears inadvertently overdosed with xylazine (especially during hibernation). Taylor et al. (1982) used M50-50 to increase the respiratory rate of a polar bear whose breathing was severely depressed by M99. Xylazine also reduces respiratory rate (Haver-Lockhart, package insert), so severe overdoses of this drug could cause respiratory failure. Hatch et al. (1982) and Mech et al. (1985) used yohimbine to correct overdoses of xylazine in dogs and deer (*Odocoileus virginianus*), respectively. We noticed little increase in respiratory rate after injection of yohimbine, possibly because respiration was not significantly depressed by the low dose of xylazine we used. Respiratory rates were essentially the same for bears immobilized with ketamine and xylazine ($\bar{x} = 10.9 \pm 0.9$ 2 SE breaths/min, $N = 65$) as for bears immobilized with ketamine alone ($\bar{x} = 10.2 \pm 1.3$ breaths/min, $N = 40$). Ramsay et al. (1985) used higher doses of ketamine (2 times the dose we used) and xylazine (5–6 times our dose) in polar bears (to ensure that they did not recover prematurely) and observed lower respiratory rates; consequently, they recorded significant increases in respiratory rates after injection of yohimbine.

Xylazine also reduces the heart rate (Knight 1980), and yohimbine increases it. However, yohimbine apparently blocks the normal feedback of norepinephrine at the α_2 -adrenoreceptors, possibly causing higher than normal heart rates and blood pressure (e.g., see Hsu et al. 1985). This possibility should be investigated. In our study the bear given the highest dose of yohimbine (0.42 mg/kg, no xylazine) exhibited an adverse reaction (severe trembling and hyperventilation), presumably due to an excessive release of norepinephrine. In all other cases, where yohimbine was used (at lower doses) after immobilization with ketamine-xylazine, no adverse reactions were observed.

The lowest dose of yohimbine used in this study (5% of the dose of xylazine = 0.1 mg yohimbine/kg, with xylazine administered at 2 mg/kg) worked as effectively as the higher doses, indicating that this low dose may still have been more than necessary to reverse immobilization. Ramsay et al. (1985) also used an IV dose of 0.1 mg yohimbine/kg in polar bears immobilized with ketamine-xylazine, but because they used higher doses of ketamine and xylazine, their dosage of yohimbine with respect to xylazine was lower (0.3%–2%) than what we used. Recovery was hastened by these low dosages, however the median time to recovery after yohimbine injection in their study was twice (10 min) that of our study. Twenty-five percent of their bears took 20 min or more to recover.

We conclude that yohimbine administered IV at about 0.05 mg/mg xylazine is safe and effective and likely better for a bear than leaving it to recover without an antagonist. The drug is also very affordable (about \$0.03 per bear at this dosage). Yohimbine is sold by Sigma Chemical Co. (St. Louis, MO 63178) in powdered form and can be constituted in saline to 2 mg/ml or, as we learned after the completion of this study (U. S. Seal, pers. commun.), up to at least 5 mg/ml in 5% dextrose (5 mg/ml can be obtained in distilled water, but dextrose should be used to prevent hemolysis). Yohimbine is still an experimental drug, so it is not sold for use in animals that will be consumed by humans.

LITERATURE CITED

- ADDISON, E. M., AND G. B. KOLENOSKY. 1979. Use of ketamine hydrochloride and xylazine hydrochloride to immobilize black bears (*Ursus americanus*). *J. Wildl. Dis.* 15:253–258.
- BEEMAN, L. E., M. R. PELTON, AND L. C. MARCUM. 1974. Use of M99 etorphine for immobilizing black bears. *J. Wildl. Manage.* 38:568–569.
- BERTHELSEN, S., AND W. A. PETTINGER. 1977. A functional basis for classification of α -adrenergic receptors. *Life Sci.* 21:595–606.
- CLARK, J. T., E. R. SMITH, AND J. M. DAVIDSON. 1984. Enhancement of sexual motivation in male rats by yohimbine. *Science* 225:847–849.
- GOLDBERG, M. R., AND D. ROBERTSON. 1983. Yohimbine: a pharmacological probe for study of the α_2 -adrenoreceptor. *Pharmacol. Rev.* 35:143–180.
- HAIGH, J. C., I. STIRLING, AND E. BROUGHTON. 1985. Immobilization of polar bears (*Ursus maritimus* Phipps) with a mixture of tiletamine hydrochloride and zolazepam hydrochloride. *J. Wildl. Dis.* 21:43–47.
- HATCH, R. C., AND T. RUCH. 1974. Experiments on antagonism of ketamine anesthesia in cats given adren-

- ergic, serotonergic, and cholinergic stimulants alone and in combination. *Am. J. Vet. Res.* 35:35-39.
- , N. H. BOOTH, J. D. CLARK, L. M. CRAWFORD, JR., J. V. KITZMAN, AND B. WALLNER. 1982. Antagonism of xylazine sedation in dogs by 4-aminopyridine and yohimbine. *Am. J. Vet. Res.* 43:1009-1014.
- , J. V. KITZMAN, B. M. WALLNER, AND J. D. CLARK. 1983. Antagonism of ketamine anesthesia in cats by 4-aminopyridine and yohimbine. *Am. J. Vet. Res.* 44:417-423.
- HOFFMAN, B. B., AND R. J. LEFKOWITZ. 1980. Alpha-adrenergic receptor subtypes. *N. Engl. J. Med.* 302:1390-1396.
- HSU, W. H. 1981. Xylazine-induced depression and its antagonism by alpha-adrenergic blocking agents. *J. Pharmacol. Exp. Ther.* 218:188-192.
- . 1983. Effect of yohimbine on xylazine-induced central nervous system depression in dogs. *J. Am. Vet. Med. Assoc.* 182:698-699.
- , Z. LU, AND F. B. HEMBROUGH. 1985. Effect of xylazine on heart rate and arterial blood pressure in conscious dogs, as influenced by atropine, 4-aminopyridine, doxapram, and yohimbine. *J. Am. Vet. Med. Assoc.* 186:153-156.
- , AND W. P. SHULAW. 1984. Effect of yohimbine on xylazine-induced immobilization in white-tailed deer. *J. Am. Vet. Med. Assoc.* 185:1301-1303.
- HUGIE, R. D., J. LANDRY, AND J. HERNES. 1976. The use of ketamine hydrochloride as an anesthetic in black bears (*Ursus americanus*) in Maine. *Trans. N.E. Fish and Wildl. Conf.* 33:83-86.
- JESSUP, D. A., W. E. CLARK, P. A. GULLETT, AND K. R. JONES. 1983. Immobilization of mule deer with ketamine and xylazine, and reversal of immobilization with yohimbine. *J. Am. Vet. Med. Assoc.* 183:1339-1340.
- KNIGHT, A. P. 1980. Xylazine. *J. Am. Vet. Med. Assoc.* 176:454-455.
- LEE, J., R. SCHWEINSBURG, F. KERNAN, AND J. HAIGH. 1981. Immobilization of polar bears (*Ursus maritimus*, Phipps) with ketamine hydrochloride and xylazine hydrochloride. *J. Wildl. Dis.* 17:331-336.
- LYNCH, G. M., W. HALL, B. PELCHAT, AND J. A. HANSON. 1982. Chemical immobilization of black bear with special reference to the use of ketamine-xylazine. Pages 245-266 in L. Nielsen, J.C. Haigh, and M.E. Fowler, eds. *Chemical immobilization of North American wildlife*. Wisconsin Humane Soc., Inc., Milwaukee.
- MECH, L. D., G. D. DELGUIDICE, P. D. KARNS, AND U. S. SEAL. 1985. Yohimbine hydrochloride as an antagonist to xylazine hydrochloride-ketamine hydrochloride immobilization of white-tailed deer. *J. Wildl. Dis.* 21:405-410.
- MILLER, R. L., AND G. B. WILL. 1976. Use of M99 etorphine and antagonists to immobilize and handle black bears. *Int. Conf. Bear Res. and Manage.* 3:225-234.
- RAMSAY, M. A., I. STIRLING, L. Ø. KNUTSEN, AND E. BROUGHTON. 1985. Use of yohimbine hydrochloride to reverse immobilization of polar bears by ketamine hydrochloride and xylazine hydrochloride. *J. Wildl. Dis.* 21:396-400.
- RENECKER, L. A., AND C. D. OLSEN. 1986. Antagonism of xylazine hydrochloride with yohimbine hydrochloride and 4-aminopyridine in captive wapiti. *J. Wildl. Dis.* 22:91-96.
- SCHMIDT, M. J. 1983. Antagonism of xylazine sedation by yohimbine and 4-aminopyridine in an adult asian elephant (*Elaphas maximus*). *J. Zoo Anim. Med.* 14:94-97.
- STEWART, G. R., J. M. SIPERK, AND V. R. WHEELER. 1980. Use of the cataleptoid anesthetic CI-744 for chemical restraint of black bears. *Int. Conf. Bear Res. and Manage.* 4:57-61.
- STIRLING I., E. BROUGHTON, L. Ø. KNUTSEN, M. A. RAMSAY, AND D. S. ANDRIASHEK. 1985. Immobilization of polar bears with Telazol on the western coast of Hudson Bay during summer 1984. *Can. Wildl. Serv. Prog. Notes* 157. 7pp.
- TAYLOR, M. K., D. P. DEMASTER, S. P. SHELDON, AND F. E. SORENSEN. 1982. Use of M50-50 as a therapeutic drug for M99-induced trauma. *J. Wildl. Manage.* 46:252-253.