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# YOHIMBINE HYDROCHLORIDE REVERSAL OF KETAMINE HYDROCHLORIDE AND XYLAZINE HYDROCHLORIDE IMMOBILIZATION OF BENGAL TIGERS AND EFFECTS ON HEMATOLOGY AND SERUM CHEMISTRIES

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ABSTRACT: Six bengal tigers (*Panthera tigris tigris*) were immobilized five times at 2-wk intervals with ketamine hydrochloride (ketamine) and xylazine hydrochloride (xylazine) mixtures at different dose levels. Hematology and serum chemistry analyses on blood samples collected at each immobilization remained normal during the study. There were acute changes in hematocrit, chloride, potassium, glucose, and bilirubin as a function of xylazine dose level. The effect of yohimbine hydrochloride (yohimbine) on the depth and duration of immobilization was evaluated in a crossover design with every animal serving as its own control at each dose. Administration of yohimbine resulted in recovery of the animals within 4–8 min in contrast to >60 min with no yohimbine treatment. There were no adverse effects noted with the yohimbine treatment and the tigers did not exhibit a relapse over the next 24 hr. Yohimbine at a dose of 5–15 mg per adult tiger provided effective reversal of 50–150 mg of xylazine per tiger.

*Key words:* Bengal tigers, ketamine, xylazine, yohimbine, immobilization, anesthesia, hematology, blood, serum, chemistry, *Panthera tigris tigris*.

## INTRODUCTION

Published information on the drug immobilization of tigers includes reports on the use of phencyclidine in combination with promazine (Seal and Erickson, 1969; Seal et al., 1970), cyclohexanone (Bennett and Tillotson, 1969), tiletamine (Bennett et al., 1972), and ketamine and promazine (Seal et al., 1985) in captive tigers. Free-ranging tigers have been captured with CI-744 (Seidensticker et al., 1974; Smith et al., 1983) and a mixture of ketamine with acepromazine (Seal and Mech, unpubl. obs.). Recovery times of immobilized free-ranging tigers averaged 5 hr and ranged to 9 hr. These prolonged, uncontrollable recovery times are a serious disadvantage for routine use of chemical immobilization of free-ranging tigers. Also phencyclidine and tiletamine (CI-744) are not commercially available. Current practice, as described for captive and free-ranging lions, is to use ketamine with a tranquilizer or with xylazine (Bush et al., 1978; Herbst et al., 1985). We are aware of five tigers that have died with profound respiratory depression or prolonged physical depression following the use of the ketamine and xylazine combination. The availability of yohimbine as an effective antagonist for the depressant effects of xylazine and its successful use in the domestic cat (Hatch et al., 1983; Hsu and Lu, 1984) and several wild species (Jacobson et al., 1985; Mech et al., 1985; Ramsay et al., 1985; Kreeger and Seal, 1986a) suggested the study of yohimbine's effects as an antagonist for xylazine in tigers.

## METHODS

The studies were performed at the Henry Doorly Zoo between January and April 1986. The five female and one male adult tigers ranged in age from 4 to 7 yr. They were housed separately in indoor pens, 3 × 7 m. Building temperature was maintained at 20–22 C, with a photoperiod provided by outdoor light. They were fed a commercial feline diet 5 days a week with water available ad libitum. There was no significant change in body weight during the study. The tigers were fasted overnight prior to immobilization but water was available. One of



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TABLE 1. Immobilization of Bengal tigers with ketamine and xylazine followed by reversal with yohimbine.

| Measure | Xylazine, mg/kg (*n*) | | | | |
|---|---|---|---|---|---|
| | 0.3 (18) | | 1.0 (12) | | |
| | Mean | SE | Mean | SE | $P <$ |
| Ketamine (mg/animal) | 570.0 | 32.0 | 350.0 | 26.0 | 0.001 |
| Xylazine (mg/animal) | 42.0 | 1.7 | 142.0 | 6.0 | 0.001 |
| Induction time (min) | 27.4 | 1.8 | 25.3 | 2.5 | NS[a] |
| Control recovery stage[b] | 1.8 | 0.3 | 1.0 | 0 | NS |
| Stimulation response[b] | 2.6 | 0.3 | 1.4 | 0.2 | 0.06 |
| Yohimbine (mg/animal) | 4.5 | 0.4 | 13.6 | 1.1 | 0.001 |
| Yohimbine response[b] | 5.0 | 0.0 | 5.0 | 0 | NS |
| Yohimbine up time (min) | 8.2 | 0.4 | 4.1 | 1.1 | 0.01 |
| Control up time (min) | 60+ | | 60+ | | |

[a] Not significant.

[b] Recovery in controls was judged at 60 min after the last ketamine injection based upon 5 stages: 1, lateral recumbency; 2, lateral recumbency with head up; 3, sternal recumbency; 4, sitting; and 5, walking. The animal was then stimulated by two firm pushes with a stick on the rear quarters and the response noted in terms of the above five point scale of recovery stages. The response to yohimbine, on this five point scale, was recorded at 20–30 min after i.v. administration of the yohimbine.

the tigers was treated for an infected claw during the study. Yohimbine (Sigma Chemical Co., P.O. Box 14508, St. Louis, Missouri 63178, USA) solution for injection was prepared, at the beginning of the study, by dissolving the salt in sterile distilled water at a final concentration of 5 mg/ml by warming to 50 C and then adding sterile 50% glucose to a final concentration of 5%. It was stored in a refrigerator.

The immobilizing drugs were administered by hand injection to four of the tigers while restrained in a squeeze cage. A blowgun was used for the other two tigers. Each animal was immobilized, at 2-wk intervals, twice with 5 ± 0.3 mg/kg ketamine 100 mg/ml (Ketaset, Bristol Laboratories, Syracuse, New York 66201, USA) and 0.3 ± 0.02 mg/kg xylazine, 100 mg/ml (Rompun, Haver-Lockhart, Bayvet Division, Cutter Laboratories, Inc., Ft. Dodge, Iowa 50501, USA) and spontaneous recovery observed. The same dosages were repeated and 4.5 ± 0.4 mg/animal of yohimbine was administered intravenously (i.v.) at 30 min after the last dose of ketamine and recovery observed. The next two immobilizations were with 1.0 ± 0.05 mg/kg of xylazine and a 30% reduction of the ketamine dose (3.5 ± 0.2 mg/kg). Yohimbine, 15 mg/animal i.v., was used for reversal in one of these immobilizations. In each immobilization the xylazine was administered first, followed by ketamine at 10 min. Time to immobilization was recorded when the animal was recumbent and would not lift its head when touched.

Recovery in controls was judged at 60 min after the last ketamine injection based upon five stages; 1, lateral recumbency; 2, lateral recumbency with head up; 3, sternal recumbency; 4, sitting; and 5, walking. The animal was then stimulated by two firm pushes with a stick on the rear quarters and the response noted in terms of the above five point scale of recovery stages.

The tigers were weighed. Pulse, temperature, and respiration were measured, and a blood sample collected. The hematology and serum chemistry analyses were conducted within 24 hr at a local pathology laboratory. Statistical comparisons were made by one-way ANOVA with $P \leq 0.05$ accepted as significant.

## RESULTS

The dose of ketamine required for comparable depth of immobilization, as measured by induction time, was reduced 30% at the high dose of xylazine (Table 1). Induction time was made comparable for both xylazine dose levels by adjustment of the ketamine dose. The depth of anesthesia at 60 min after the last injection of ketamine was slightly less at the lower dose of xylazine for the animals receiving no yohimbine, but they were still depressed (Table 1). Intravenous administration of yohimbine resulted in an increase of respiration within 2 min, followed by full recovery within 4–8 min in contrast to the prolonged recovery (>60 min) without the antagonist.

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TABLE 2. Baseline physiology and hematology data in Bengal tigers immobilized with ketamine and xylazine.

| Assay | Units | *n* | Mean | SE |
|---|---|---|---|---|
| Weight | kg | 6 | 115.5 | 1.0 |
| Respiration | per min | 25 | 12.8 | 1.8 |
| Pulse | per min | 25 | 78.0 | 1.9 |
| Temperature | deg C | 23 | 38.3 | 0.1 |
| Hemoglobin | g/dl | 26 | 12.1 | 0.9 |
| Red cells | $10^6/\mu l$ | 26 | 6.1 | 0.5 |
| Hematocrit | vol % | 26 | 34.8 | 2.6 |
| MCV | fl | 26 | 56.9 | 1.6 |
| MCH | pg | 26 | 19.8 | 0.8 |
| White cells | $10^3/\mu l$ | 26 | 10.5 | 3.1 |
| Neutrophils | $10^3/\mu l$ | 26 | 7.7 | 1.9 |
| Lymphocytes | $10^3/\mu l$ | 26 | 1.8 | 0.9 |

TABLE 3. Baseline blood chemistry data on 30 samples collected 10 min after induction from six Bengal tigers immobilized with ketamine and xylazine.

| Assay | Units | Mean | SE |
|---|---|---|---|
| Na | meq/liter | 146.8 | 0.30 |
| Cl | meq/liter | 122.1 | 0.50 |
| K | meq/liter | 4.0 | 0.03 |
| $CO_2$ | meq/liter | 18.2 | 0.30 |
| Anion gap | meq/liter | 6.6 | 0.40 |
| Osmolality | meq/liter | 297.0 | 0.70 |
| BUN | mg/dl | 23.4 | 0.70 |
| Creatinine | mg/dl | 2.5 | 0.10 |
| BUN/Cr ratio | | 9.7 | 0.60 |
| Glucose | mg/dl | 121.7 | 3.00 |
| Serum protein | g/dl | 6.9 | 0.10 |
| Albumin | g/dl | 3.5 | 0.03 |
| Calcium | mg/dl | 10.2 | 0.10 |
| Phosphorus | mg/dl | 5.4 | 0.10 |
| Cholesterol | mg/dl | 225.0 | 3.60 |
| Triglycerides | mg/dl | 30.2 | 2.00 |
| Bilirubin | mg/dl | 0.4 | 0.02 |
| Alkaline phosphatase | IU | 24.2 | 0.40 |
| LDH | IU | 230.0 | 12.30 |
| AST | IU | 26.5 | 4.70 |

There was no change in body weight in any of the animals during the 3 mo of the study (Table 2). The two dose levels of xylazine produced no significant difference in respiration rate, pulse rate, and body temperature as measured immediately after the animals were immobilized. Serial data were not collected. One animal vomited several times about 5–8 min after each xylazine injection. Another animal vomited on one occasion. Hematology, except for hematocrit, was not affected by dose level of xylazine and there were no changes during the study (Table 2). Baseline chemistry values did not change during the study (Table 3), but the higher dose of xylazine produced an acute increase in hematocrit, potassium, glucose, and bilirubin and a decrease in chloride (Table 4).

## DISCUSSION

Yohimbine was an effective antagonist to xylazine used with ketamine for immobilization of these six Bengal tigers. Recovery was observed within 10 min of treatment with the antagonist in contrast to >60 min for animals allowed to recover spontaneously. Data from studies on cats (Hatch et al., 1983) and wolves (Kreeger and Seal, 1986b) indicate that the effect of yohimbine on the catalepsy of ketamine anesthesia is minimal although it may produce arousal. Observation of the tigers for 48 hr following immobilization and reversal did not indicate any return to a depressed state.

There was no indication of adverse effects of the yohimbine treatments from the body weight, hematology, and blood chemistry data. The minimal, but significant changes in blood chemistry associated with the higher dose of xylazine are consistent with reports of hyperglycemia and glycosuria following use of this drug in domestic species (Symonds, 1976). The consistent vomiting in one tiger is a characteristic dose dependent effect of xylazine (Lucot and Crampton, 1986).

Yohimbine eliminates the prolonged depression following use of xylazine for immobilization. Use of yohimbine in immobilized tigers has provided prompt recovery on two occasions of severe respiratory depression characterized by arrest and failure to return to spontaneous respiration. The timing of the treatment with yohimbine following the last ketamine injection will determine whether residual ef-

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TABLE 4. Hematology and blood chemistry assays affected by xylazine dosage in Bengal tigers immobilized with ketamine and xylazine.

| | Xylazine dose, mg/kg (*n*) | | | | | |
|---|---|---|---|---|---|---|
| | 0.3 (18) | | 1.0 (12) | | | |
| Assay | Mean | SE | Mean | SE | *F* | *P* < |
| Hematocrit | 33.9 | 0.40 | 36.1 | 0.6 | 4.10 | 0.05 |
| Chloride | 123.0 | 0.60 | 120.7 | 0.8 | 5.88 | 0.02 |
| Potassium | 3.9 | 0.04 | 4.1 | 0.1 | 6.35 | 0.02 |
| Glucose | 114.5 | 2.70 | 132.4 | 7.2 | 8.00 | 0.01 |
| Bilirubin | 0.4 | 0.02 | 0.5 | 0.5 | 10.04 | 0.001 |

fects of ketamine anesthesia (hypersalivation, rigidity, ataxia, excitability) are observed. This response will be minimized by allowing sufficient time for the ketamine to be metabolized—about 30 min depending upon the size of the last ketamine dose. We have found the use of yohimbine as an antagonist to xylazine in tigers valuable in producing shorter recovery times and quickly reversing episodes of severe respiratory depression (Seal, Armstrong, and Simmons unpubl. obs.).

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