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# YOHIMBINE REVERSAL OF KETAMINE-XYLAZINE IMMOBILIZATION OF RACCOONS (*PROCYON LOTOR*)

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ABSTRACT: Six adult raccoons (*Procyon lotor*) were sedated with a combination of ketamine hydrochloride (KH) at 10 mg/kg body weight and xylazine hydrochloride (XH) at 2 mg/kg body weight intramuscularly (i.m.). Twenty min after the KH-XH combination was given, yohimbine hydrochloride (YH) at either 0.1 mg/kg (Trial 1) or 0.2 mg/kg (Trial 2) body weight or a saline control (Trial 3) was administered intravenously (i.v.). The time to arousal, time to sternal recumbency and time to walking were recorded. These times were significantly shortened after YH administration [e.g., mean time to walking (MTW) at 0.2 mg/kg YH = 23.7 min] as compared to the saline controls (MTW = 108.8 min). Heart and respiratory rates both increased after YH administration, while body temperature remained constant. A fourth trial was performed using a higher ratio of KH to XH (45:1 rather than 5:1) to mimic sedation as performed in the field. The mean time to arousal (MTA) and MTW in this trial (1.3 and 23.7 min, respectively) were significantly shorter than controls and similar to YH trials performed after immobilization with 5:1 KH-XH. Yohimbine hydrochloride may be useful in field studies that require sedation of raccoons using KH-XH combinations.

*Key words:* Ketamine hydrochloride, raccoon, *Procyon lotor*, xylazine hydrochloride, yohimbine hydrochloride, chemical immobilization, experimental study.

## INTRODUCTION

Raccoon (*Procyon lotor*) rabies, formerly concentrated in Florida and Georgia, has grown to epizootic proportions in the Mid-Atlantic region of the United States since 1977. Field study of rabies epidemiology and specific methods for its control, such as oral immunization (Rupprecht et al., 1986), necessitate the live-capture and sedation of relatively large numbers of raccoons. Concern over the duration of field sedation and the potential vulnerability of raccoons to predation and environmental stress while in this state, prompted a study designed to shorten the recovery period. Yohimbine hydrochloride (YH) has been tested in a wide variety of wild and domestic animal species, including white-tailed deer (*Odocoileus virginianus*) (Hsu and Shulaw, 1984; Mech et al., 1985), mule deer (*O. hemionus*) (Jessup et al., 1983, 1985), elk (*Cervus elaphus*) (Renecker and Olsen, 1986), domestic cattle (Kitzman et al., 1982), african elephant (*Loxodonta africana*) (Jacobsen et al., 1985), asian elephant (*Elaphus maximus*) (Schmidt, 1983), domestic cat (Hatch et al., 1983, 1984; Hsu and Lu, 1984), Bengal tiger (*Panthera tigris*) (Seal et al., 1987), polar bear (*Ursus maritimus*) (Ramsay et al., 1985), black bear (*U. americanus*) (Garshelis et al., 1987), domestic dog (Wallner et al., 1982; Cronin et al., 1983; Hatch et al., 1985; Hsu, 1985), coyote (*C. latrans*) (Kreeger and Seal, 1986a), gray wolf (*C. lupus*) (Kreeger and Seal, 1986b), and guinea fowl (*Numida meleagris*) (Teare, 1987). Yohimbine hydrochloride effectively reverses sedation induced by a number of pharmacological agonists, including xylazine hydrochloride (XH), but its specific effects in small wild carnivores have not been reported. Yohimbine hydrochloride has known alpha-2 adrenergic antagonist action and directly reverses the alpha-2 agonist effects of XH. Yohimbine hydrochloride may partially antagonize ketamine hydrochloride (KH), yet had no effect on KH sedation in the gray wolf (Kreeger and Seal, 1986b) or black bear (Garshelis et al., 1987). The purpose of our study was to develop a protocol by which the recovery period could be shortened using YH in raccoons sedated with a KH-XH combination.

## MATERIALS AND METHODS

Four adult female and two adult male raccoons live-trapped (Tomahawk Live Trap, Tomahawk, Wisconsin 54487, USA) in a raccoon-rabies-free area of southeastern Pennsylvania were maintained in individual stainless-steel primate squeeze cages (Allentown Caging, Allentown, New Jersey 08501, USA) on a commercial dry feline diet (Purina Cat Chow, Mechanicsburg, Pennsylvania 17011, USA); water was available ad libitum. All raccoons were immunized against rabies (Immrab®, Pitman-Moore, Inc., Washington Crossing, New Jersey 08560, USA), canine distemper, parvovirus, canine hepatitis and leptospirosis (Duramune®, Fort Dodge Laboratories, Fort Dodge, Iowa, 50501 USA) using commercial vaccines. Each animal was weighed to the nearest 0.1 kg prior to inclusion in the study. The mean weight of the raccoons was 7.5 ± 0.7 kg. During August 1987, four immobilization trials were performed on each animal, each separated by at least 4 days. The animals were inoculated in squeeze cages using KH-XH given together by hand-held syringe and subsequently brought outside to a wire-enclosed pen with a grass floor (4.5 $m^2$) where they were given YH (Sigma Chemical Co., St. Louis, Missouri 63178, USA) antagonist and were allowed to recover from sedation, as described below. The YH solution was prepared in a sterile 5% dextrose solution, as described previously (Kreeger et al., 1987).

### Trials 1, 2 and 3

Each raccoon received an intramuscular (i.m.) combination of KH (Ketaset®, Bristol Laboratories, Syracuse, New York 13201, USA) at 10.0 mg/kg body weight and XH (Rompun®, Haver-Lockhart Laboratories, Shawnee, Kansas 66201, USA) at 2.0 mg/kg body weight in either the gluteal or quadriceps muscles. Induction time was recorded as the time interval from KH-XH inoculation until the animal was recumbent and no longer responsive to tactile or auditory stimuli. Sedation was judged adequate if the animal gave no response to a toe pinch. Lacri-Lube® (Allergan Pharmaceuticals, Inc., Irvine, California 92713, USA) was used to moisten the eyes and prevent corneal ulceration. At this time, resting heart rate, respiratory rate and rectal temperature were recorded and the animal was moved to the outdoor pen.

While outdoors, raccoons were again checked for adequate sedation, and at 20 min post-KH-XH administration, YH was given intravenously (i.v.) via the jugular vein. Jugular injection of YH was facilitated by using a small diameter needle (≤25 gauge) and a steady injection flow so as not to "push" the vein off the needle. Each raccoon received either 0.1 mg/kg (Trial 1) or 0.2 mg/kg YH (Trial 2) or a 1.0 ml volume of physiological saline (Trial 3) per trial; by the end of the third trial, each raccoon had received both doses of YH and the saline control. In this way, each animal served as its own control. Heart rate, respiratory rate, and body temperature were again monitored postantagonist or saline administration and recorded at 2 min after antagonist administration.

The time to arousal was recorded as the time from YH or saline administration until the animal could raise its head and was aware of tactile or auditory stimuli. The time to sternal recumbency was measured from YH or saline administration until the animal repositioned itself in sternal recumbency if moved from that position. Lastly, the time to walking was recorded from YH or saline administration until the animal could walk in coordinated movements away from auditory/visual stimuli. Raccoons were monitored thereafter for any adverse clinical signs, relapses into sedation or abnormal behavior.

### Trial 4

Raccoon weights in the field are only estimated prior to sedation. In bait-biomarker studies of raccoons in the field, Rupprecht et al. (1986) sedated "averaged-sized" raccoons with 90 mg KH and 2 mg XH. Thus, Trial 4 was designed to test the effects of YH on raccoons sedated with this higher ratio of KH to XH. The raccoons were given the above dosage initially, and if induction was not complete, another one-half dosage of the KH-XH combination was given i.m. until sedation was judged adequate. Yohimbine hydrochloride was given i.v. at 20 min after KH-XH at a dose of 0.2 mg/kg body weight. Heart rate, respiratory rate, and body temperature were monitored before and after antagonist.

Statistical analyses were calculated using ANOVA at the $P < 0.05$ significance level; means are reported with standard error (SE). If significant differences were found, means were compared by the modified least-significant-difference test (Winer, 1971).

## RESULTS

The mean induction time for KH:XH sedation ($n = 24$) was 3.5 ± 0.7 min. Both the mean time to arousal (MTA) and mean time to walking (MTW) were significantly decreased in all groups of KH-XH-sedated raccoons given YH compared to saline controls ($P < 0.05$), when either dose of the YH antagonist was used (Table 1). For

TABLE 1. Mean (±SE) times to arousal (MTA), walking (MTW) and heart rates (MHR) of raccoons immobilized i.m. with ketamine (KH) and xylazine (XH) and antagonized i.v. with yohimbine (YH) 20 min postsedation.

| I.v. antagonist | MTA (min) | MTW (min) | MHR (beats/min)[b] |
|---|---|---|---|
| Saline control | 91.3 ± 20.7 | 108.8 ± 21.6 | 94.7 ± 7.0 |
| YH (0.1 mg/kg) | 8.9 ± 2.8[a] | 24.8 ± 4.9[a] | 155.3 ± 29.1 |
| YH (0.2 mg/kg) | 5.5 ± 2.2[a] | 23.7 ± 6.0[a] | 219.2 ± 13.0[a] |
| YH (0.2 mg/kg at field dose of KH-XH) | 1.3 ± 0.6[a] | 23.7 ± 4.6[a] | 250.0 ± 13.2[a] |

[a] Denotes those means which were significantly different ($P < 0.05$) from saline controls in each respective column.
[b] Measured at 2 min post-YH or saline administration.

example, YH at 0.1 or 0.2 mg/kg reduced the MTW from 109 min for controls to approximately 24 min. Neither the MTA nor the MTW changed significantly between the 0.1 and 0.2 mg/kg doses of YH.

Resting heart rate after KH-XH induction ranged from 66 to 166 (mean = 94.7 ± 17.1) beats/min, but increased rapidly after YH administration to a peak rate which plateaued within approximately 2 min and was dose-related (Table 1). Although the effect upon mean heart rate (MHR) at 2 min after YH using the 0.1 mg/kg dose was not statistically detectable from the saline control, the 0.2 mg/kg dose was highly significantly different from the control ($P < 0.0001$) at both the calculated and field dosages of KH-XH. No significant differences in MHR were found between Trials 3 and 4, but both were significantly elevated over MHR in Trial 2. Heart rate remained constant after administration of intravenous saline control.

Respiratory rate also appeared to increase after administration of YH, but was difficult to quantify because breathing became very shallow and shortened. It was not possible to assess whether these were true breaths or were due to the excitatory phase of recovery from anesthesia. Rectal temperatures did not vary after either administration of YH or the saline control. The mean and range of rectal temperatures pre- and postantagonist were 39.2 C (37.8 to 40.1 C) and 39.2 C (37.8 to 40.1 C), respectively.

During the first 2 min after injection, except for the initial rapid increase in heart rate, no changes in attitude were apparent. Thereafter, raccoon behavior was fairly stereotypical: muzzle licking prior to eye opening; random, fixed staring at surroundings; finally attaining a sternal posture from dorsal recumbency.

## DISCUSSION

Xylazine hydrochloride is an alpha-2 adrenergic agonist. Its action inhibits norepinephrine release from presynaptic neural sites by activating presynaptic alpha-2 adrenoceptors, causing a negative feedback mechanism to prevent further release of norepinephrine. Yohimbine hydrochloride is an alpha-2 antagonist and therefore antagonizes the alpha-2 receptor to again allow for the release of norepinephrine (Hoffman and Lefkowitz, 1980; Goldberg and Robertson, 1983).

Yohimbine hydrochloride may partially antagonize the effects of KH (Kreeger and Seal, 1986a). Ketamine hydrochloride has been implicated to have action at several different receptor sites including cholinergic, seritonergic, opiod and N-methyl-aspartic receptor sites (Finck and Ngai, 1982; White et al., 1982; Anis et al., 1983; Leeuwin et al., 1984; Kreeger et al., 1987). It has known sites of action in the central nervous system at the thalamoneocortical projecting system, arousal activity in the hippocampus and stimulation of the sympathetic nervous system, which may be due to interference with re-uptake of norepinephrine (A. Klide, pers. comm.). The partial antagonist effects of YH toward KH sedation may occur because YH blocks only

some of the receptor types or it may act as a general nervous system stimulant (Hsu and Lu, 1984; Kreeger and Seal, 1986b). Evidence for the latter was shown in gray wolves sedated only with KH. The arousal times of the wolves were significantly shortened but walk times were not different from controls (Kreeger and Seal, 1986b). In all four trials, raccoons were aware of their surroundings from 1 to 9 min after YH administration, however, they could not walk in a coordinated manner until 24 min post-YH. This may be attributed to the residual effect of KH after XH has been fully antagonized.

In Trial 4 of our study, the KH:XH ratio (45:1) was nine times greater than in the first three trials with a dosage of 142.5 mg KH and 3.2 mg XH. The MTW was significantly shortened as compared to controls and essentially identical to the MTW at the lower ratio of KH to XH (5:1) which averaged 75 mg KH and 15 mg XV. This suggests that YH may have some definitive action in reversing KH sedation in raccoons since the MTW is the same but the dosage of KH is almost doubled.

The lower ratio of KH to XH (5:1) was used in the first three trials because of a concern that KH effects would not be reversed at all by YH. This ratio of KH:XH caused a more erratic induction than the KH:XH ratio typically used in the field. Several raccoons experienced a hyperreflexive stage or had small episodes of spasms directly after induction. These spasms involved very short (<1 min) periods of thoracic twitching. The lower ratio of KH:XH also caused vomition in 33% (6/18) of the sedations. This is not unexpected since XH has known emetic side-effects in domestic dogs and cats. In previous studies using the field dosages of KH:XH, vomition on induction had never been observed. Tarry feces were seen in four of the study animals on the day following sedation with 5:1 dosages. Its relationship to YH administration was improbable, because it was seen also in animals receiving only the saline control on that day. Due to these observed side effects, we recommend using a KH:XH ratio above 5:1 in raccoons.

The marked increase in heart rate following YH administration appeared dose-related. This finding may be attributed to several mechanisms. Xylazine hydrochloride may initiate bradycardia while KH causes sympathetic stimulation to increase the heart rate. When XH is completely antagonized, the KH effect may go unchecked and sympathetic stimulation may increase the heart rate without XH to decrease it. Yohimbine hydrochloride, itself, may act to increase heart rate by blocking alpha-2 adrenergic receptors, enhancing neural release of norepinephrine, and causing hypotension (Goodman and Gilman, 1975).

This study has demonstrated the effectiveness of YH to reverse KH-XH sedation in raccoons. No adverse effects were seen after YH administration except for the increased heart rate. Although YH appears relatively safe in raccoons, it has resulted in convulsions and at least one death in a polar bear (Ramsay et al., 1985), severe trembling and hyperventilation in a black bear (Garshelis et al., 1987), twitching in coyotes (Kreeger and Seal, 1986a), and hyper/hypotension and cardiac arrhythmias (tachycardia) in domestic animals (Sanghvi and Gershon, 1970; Hatch, 1973; Hatch and Ruch, 1974; Goldberg and Robertson, 1983). The potential drawback of the tachycardia in raccoons can be minimized by administering only the 0.1 mg/kg dosage of YH. Higher doses significantly increase the heart rate with no decrease in time to walking. This increase in heart rate may be minimized by making careful weight measurements postsedation and administrating YH at a dose of 0.1 mg/kg body weight. This disadvantage is outweighed by the utility of YH in decreasing the length of sedation for resumption of normal activity (e.g., lactation, foraging, etc.) and diminishing the overall vulnerability of raccoons in the field. Further studies are indicated which would use this method in the field on free-ranging rather than captive raccoons, as well as to

evaluate YH efficacy by other administrative routes or in other environmental conditions.

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