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Source: Journal of Wildlife Diseases, 23(2) : 301-305

Published By: Wildlife Disease Association

URL: https://doi.org/10.7589/0090-3558-23.2.301

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Journal of Wildlife Diseases, 23(2), 1987, pp. 301–305
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ANTAGONISM OF XYLAZINE HYDROCHLORIDE–KETAMINE HYDROCHLORIDE IMMOBILIZATION IN GUINEAFOWL (*NUMIDA MELEAGRIS*) BY YOHIMBINE HYDROCHLORIDE

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ABSTRACT: The mean time to arousal (MTA), the mean time to sternal recumbency (MTSR) and the mean time to walking (MTW) were measured in 10 adult guineafowl (*Numida meleagris*) immobilized with a combination of xylazine hydrochloride (1 mg/kg) and ketamine hydrochloride (25 mg/kg). Yohimbine hydrochloride, given intravenously (1 mg/kg) at 40 min after the injection of the xylazine-ketamine, significantly shortened the MTA, the MTSR and the MTW compared to saline controls. Increasing the dosage of yohimbine to 2.5 mg/kg did not shorten recovery when compared to the lower dosage. No adverse effects were noted at either dosage of yohimbine. Yohimbine appeared to be a safe and effective antagonist of xylazine-ketamine immobilization in guineafowl and may prove useful in other avian species to produce more rapid recovery from xylazine-ketamine immobilization, xylazine sedation or xylazine overdosage.

Key words: Xylazine, ketamine, yohimbine, guineafowl, *Numida meleagris*, immobilization, antagonism.

INTRODUCTION

Yohimbine hydrochloride is an alpha-adrenergic antagonist that mainly affects alpha-2 receptors. This naturally-occurring alkaloid has received extensive study in mammals as a potential antagonist to several tranquilizing and anesthetic agents. In particular, yohimbine has been used for reversing the effects of xylazine. It effectively antagonizes xylazine, xylazine-acepromazine, xylazine-atropine sedation and xylazine-pentobarbital anesthesia in dogs and xylazine sedation in cattle (Kitzman et al., 1982; Wallner et al., 1982; Cronin et al., 1983; Hatch et al., 1985; Hsu, 1985). Yohimbine also antagonizes the effects of acepromazine and significantly reduces recovery times in cats anesthetized with meperidone-acepromazine-pentobarbital or acepromazine-pentobarbital (Hatch et al., 1984a, b). In non-domestic species, yohimbine has been used to antagonize xylazine sedation in white-tailed deer (*Odocoileus virginianus*), mule deer (*Odocoileus hemionus*) and bighorn sheep (*Ovis canadensis nelsoni*) (Hsu and Shulaw, 1984; Jessup et al., 1985) and xylazine-ketamine anesthesia in mule deer, white-tailed deer and polar bears (*Ursus maritimus*) (Jessup et al., 1983; Mech et al., 1985; Ramsey et al., 1985).

In avian species, yohimbine has received much less attention despite the use of xylazine and xylazine-ketamine for sedation and immobilization of these species (Fowler, 1978; Amand, 1980). However, Hsu (1981) has shown that pretreating 1–3-day-old leghorn chicks with 1 mg/kg of yohimbine completely abolished the sedative effects of xylazine (given at 10 mg/kg). The same study showed a significant reduction in the xylazine-induced loss of righting reflex when the chicks were pretreated with as little as 0.03 mg/kg of yohimbine. The present study was undertaken to determine whether yohimbine would safely and effectively antagonize xylazine-ketamine anesthesia in an avian species.

MATERIALS AND METHODS

Ten adult guineafowl (*Numida meleagris*), six males and four females, were used. The birds were part of a larger population that was free-ranging within the grounds of the Omaha zoo. During the study, the birds were held in a 3 ×

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TABLE 1. Effect of saline and yohimbine hydrochloride on xylazine hydrochloride–ketamine hydrochloride immobilization of guineafowl.

Trial (*n*)	Dosage	MTA[a] ± SD (min)	MTSR[b] ± SD (min)	MTW[c] ± SD (min)
Saline (10)	0.1 ml/kg	35.6 ± 18.7	50.7 ± 22.2	78.6 ± 26.1
Yohimbine (10)	1.0 mg/kg	1.4 ± 0.7[d]	28.6 ± 14.0[e]	41.5 ± 11.2[f]

[a] Mean ± SD of the time from injection of antagonist until arousal.
[b] Mean ± SD of the time from injection of antagonist until the bird could maintain sternal recumbency unassisted.
[c] Mean ± SD of the time from injection of antagonist until the bird was standing.
[d] Significantly different ($P < 0.005$) from saline treatment.
[e] Significantly different ($P < 0.025$) from saline treatment.
[f] Significantly different ($P < 0.01$) from saline treatment.

5 m outdoor, covered enclosure with a three-sided box (45 × 45 × 40 cm) for shelter. Feed and water were available ad libitum.

Prior to the start of the study, each bird was weighed to the nearest 20 g. Two immobilization trials were completed on each bird and five of the birds were used in a third trial. Trials occurred 5 days apart and used the same general protocol.

Each bird was injected in the pectoral muscles with xylazine hydrochloride (Rompun, Bayvet Division, Miles Laboratory, Inc., Shawnee, Kansas 66201, USA) at 1 mg/kg, followed immediately by ketamine hydrochloride (Ketaset, Bristol Laboratories, Syracuse, New York 13201, USA) at 25 mg/kg. The stock solution of xylazine (20 mg/ml) was diluted to 10 mg/ml with sterile saline to facilitate accurate measurement of doses. After injection of the xylazine-ketamine, the birds were released within the holding pen and the time until lateral recumbency was measured. The xylazine-ketamine dosage was based on clinical experience and was chosen to produce a depth and length of anesthesia suitable for minor surgical procedures, such as laparoscopy.

The solution of yohimbine HCl (Sigma Chemical Co., St. Louis, Missouri 63178, USA) was prepared at a concentration of 10 mg/ml in deionized water. Complete dissolution of the yohimbine required warming with constant stirring. Precipitation did not occur upon cooling to room temperature. The solution was passed through a 0.2 μm filter into evacuated sterile tubes for storage. In all trials, the antagonist (yohimbine or saline) was injected at 40 min after the xylazine-ketamine injections. Injection of the antagonist was given intravenously as rapidly as possible via the cutaneous ulnar vein. The birds were then observed until they were able to stand.

For the first trial, birds were selected randomly to receive either yohimbine at 1 mg/kg or an equivalent volume of sterile saline (0.1 ml/kg). The measured variables included the time to lateral recumbency following injection of the xylazine and ketamine and the times from antagonist injection to arousal (eyes open, head raised and responsive to stimuli), to sternal recumbency and to walking.

In subsequent trials, each bird received the same dose of xylazine and ketamine (as in the first trial), but a different intravenous treatment. In the second trial, birds received the opposite solution that was received in the first trial. In this way, each bird served as its own control. In the final trial, all the immobilized birds received intravenous yohimbine but at a higher dose of 2.5 mg/kg. Onset of immobilization and recovery times were measured as in the first trial.

Statistical analysis included calculation of the mean time to lateral recumbency (MTLR), the mean time to arousal (MTA), the mean time to sternal recumbency (MTSR) and the mean time to walking (MTW) for the control (saline) and each of the yohimbine treatments. The paired *t*-test was used to test the hypothesis that yohimbine at 1 mg/kg significantly reduced recovery times over saline-treated birds. For the birds receiving the high and low dose yohimbine, the paired *t*-test was used also to test whether the higher yohimbine dosage shortened recovery times when compared to the low yohimbine dosage.

RESULTS

Xylazine and ketamine at the dosage used in this study produced a rapid onset of immobilization in guineafowl. In all birds, lateral recumbency occurred within 1 to 6 min after the injection of xylazine and ketamine and the overall MTLR (combined trials) was 2.5 ± 1.2 min (mean ± SD). The anesthesia was judged

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TABLE 2. Effect of high and low dosage yohimbine hydrochloride on xylazine hydrochloride–ketamine hydrochloride immobilization of guineafowl.

Trial (n)	Dosage	MTA[a] ± SD (min)	MTSR[b] ± SD (min)	MTW[c] ± SD (min)
Yohimbine (5)[d]	1.0 mg/kg	1.2 ± 0.4	30.2 ± 13.1	42.0 ± 10.3
Yohimbine (5)	2.5 mg/kg	1.0 ± 0.0	30.4 ± 10.6	43.2 ± 14.3

[a] Mean ± SD of the time from injection of antagonist until arousal.
[b] Mean ± SD of the time from injection of antagonist until the bird could maintain sternal recumbency unassisted.
[c] Mean ± SD of the time from injection of antagonist until the bird was standing.
[d] Data for this trial was extracted from the data presented in Table 1 and represents the values for the five birds also tested at the higher yohimbine dosage.

adequate for many surgical procedures on the basis of little or no response to painful stimuli such as a toe pinch. Muscle relaxation produced with this dosage of xylazine-ketamine was excellent. No birds showed signs of spontaneous recovery prior to the antagonist injection. No anesthetic complications were observed in any of the immobilizations performed and all birds were alive 6 mo after completion of the trial.

Yohimbine, at either dosage, produced signs of arousal within a few minutes of injection, while saline had no such effects. The MTA for the saline treatment was 35.6 ± 18.7 min (Table 1). In the same birds, the MTA was shortened significantly to 1.4 ± 0.7 min following i.v. yohimbine at 1 mg/kg ($P < 0.005$). Similarly, yohimbine at 1 mg/kg significantly shortened the MTSR from 50.7 ± 22.2 min to 28.6 ± 14.0 min ($P < 0.025$) and the MTW from 78.6 ± 26.1 min to 41.5 ± 11.2 min ($P < 0.01$).

The higher dosage of yohimbine did not result in a significant change in the recovery times measured (Table 2). No serious adverse effects, such as convulsions, were observed at either dosage of yohimbine, although there was extensive vocalization from one bird following injection of yohimbine at 1 mg/kg.

DISCUSSION

Yohimbine rapidly resulted in signs of arousal in xylazine-ketamine immobilized guineafowl, but the birds still required a substantial period of time to regain the ability to stand. Hsu (1981) reported that yohimbine at 1 mg/kg completely abolished the effects of xylazine hydrochloride in leghorn chicks. The xylazine dosage used in this study was lower than that used by Hsu (1981). It is proposed that the recovery time required for the guineafowl following yohimbine is due to residual ketamine effects. Support for this explanation comes from several sources.

While yohimbine has been shown to restore ambulation within a few minutes for a variety of xylazine-ketamine immobilized mammals (Jessup et al., 1983; Mech et al., 1985; Ramsay et al., 1985), the ketamine dosages used in those reports were lower (<10 mg/kg) than the ketamine dosage used in this study (25 mg/kg). Hatch et al. (1983) examined yohimbine antagonism of ketamine anesthesia (20 mg/kg) in cats and reported that while signs of arousal occurred rapidly following injection of yohimbine, the time until the cats could stand was not significantly different from the saline controls. Mech et al. (1985) also noted a slightly longer recovery period in xylazine-ketamine-immobilized white-tailed deer compared to recovery times for xylazine-immobilized white-tailed deer (Hsu and Shulaw, 1984) and proposed that this was due to the concurrent usage of ketamine. Finally, yohimbine has little or no effect on recovery of psittacines immobilized with ketamine alone (Teare, unpubl. data).

In this study, the high yohimbine dosage

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did not significantly alter recovery times in xylazine-ketamine immobilized guineafowl (when compared to the low yohimbine dosage). This is evidence for a dose/response plateau with yohimbine; beyond this plateau there is no benefit of increased dosages. Mech et al. (1985) reported the same phenomenon for yohimbine in white-tailed deer. From the present study, it is only possible to conclude that the plateau for the effect of yohimbine in guineafowl is ≤ 1 mg/kg. As the potential for toxicity or other adverse effects increases with increasing dosage it is desirable to use the minimum effective dosage.

Adverse effects associated with the administration of yohimbine are rare, but have been reported. Yohimbine antagonism of xylazine-ketamine immobilization in horses resulted in rolling, repeated attempts to stand, head weaving, sweating, vocalization, ataxia once standing, and hypersensitivity to sound stimuli (Kitzman et al., 1984). High dosages of yohimbine (0.4 mg/kg) produced mild signs of excitement (piloerection, growling and barking) in two of 17 dogs (Hatch et al., 1985). In non-tranquilized cattle, yohimbine produced mild signs of arousal at low dosages (0.125 mg/kg), but mild to moderate sedation at dosages of 0.25–0.375 mg/kg (Kitzman et al., 1982). Ramsey et al. (1985) reported convulsions and death in one of 48 polar bears immobilized by xylazine-ketamine and then injected with yohimbine. In the present study, no adverse effects were associated with the use of yohimbine with the exception of prolonged vocalization in one bird given yohimbine at 1 mg/kg.

Yohimbine hydrochloride appeared to be a safe and effective antagonist for xylazine hydrochloride–ketamine hydrochloride immobilization in adult guineafowl. Arousal from anesthesia occurred within 2 min, and the time to standing was significantly shorter than in birds given saline. Further work needs to be done to clarify the minimum effective dosage of yohimbine required to arouse guineafowl from xylazine-ketamine immobilization and to determine the cardiovascular and respiratory effects of this dose of yohimbine. The effectiveness of yohimbine as an antagonist to xylazine-ketamine immobilization in this species should also encourage investigations into the effects of yohimbine on xylazine-ketamine immobilization and xylazine sedation in other avian species.

ACKNOWLEDGMENTS

The author wishes to thank Dan Cassidy for making birds and cage space available for this study. The review of this manuscript by Dr. G. Kollias is acknowledged gratefully.

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Received for publication 7 May 1986.

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