IMMOBILIZATION OF WHITE-TAILED DEER WITH XYLAZINE HYDROCHLORIDE AND KETAMINE HYDROCHLORIDE AND ANTAGONISM BY TOLAZOLINE HYDROCHLORIDE

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ABSTRACT: Fourteen penned and 17 free-ranging white-tailed deer (*Odocoileus virginianus* Rafinesque) were singularly or repeatedly immobilized with 100 mg xylazine hydrochloride (HCl) and 300 mg ketamine HCl. The mean times from intravenous injection to ambulation for 1.0, 2.0, and 4.0 mg/kg body weight doses of tolazoline HCl were 13.5, 10.5, and 9.2 min. Deer not receiving tolazoline HCl recovered in an average of 168 min. Heart rates significantly ($P < 0.001$) increased from 47 to 83 beats/min after tolazoline HCl administration, representing a return to normal rate. Tolazoline HCl had no effect on respiratory rate. A total of 85 reversals with tolazoline HCl resulted in no apparent adverse reactions.

INTRODUCTION

Until recently, the only reversible immobilizing agents available were the opioids. The opioids, however, are Schedule II controlled substances, extremely hazardous to humans, and relatively expensive on a milligram basis. With the growing necessity for handling wild animals for research or management purposes, a safe, effective, inexpensive and reversible immobilization protocol needs to be developed.

Xylazine HCl (2-(2,6-dimethylphenyl)-4H-5,6-dihydro-1,3-thiazine hydrochloride) is a non-narcotic analgesic first synthesized in Germany in 1962 (Knight, 1980). Xylazine HCl is a specific $alpha_2$-adrenergic agonist (Doxey and Roach, 1980; Docherty and Starke, 1981) providing sedation, analgesia, and myorelaxation (Booth, 1982). Depending on the species, xylazine HCl has demonstrated such ad-

verse properties as bradycardia, ruminal bloat, hyperthermia, hypotension, second-degree heart block and hyperglycemia (Antonaccio et al., 1973; Eichner et al., 1979; Young, 1979; Knight, 1980; Zingoni et al., 1982; Jensen et al., 1983). Perhaps the major disadvantage of xylazine HCl for immobilization of wildlife is an extended recovery time which could be hazardous to the animal under conditions of temperature extremes (Clark and Hall, 1969; Kitzman et al., 1982; Hsu and Schulaw, 1984).

Many cervids have been immobilized successfully with xylazine HCl, particularly when used in conjunction with the cyclohexane, ketamine HCl (Bauditz, 1972; Roughton, 1975; Wentges, 1975; Mautz et al., 1980; Jacobsen, 1983; Jessup et al., 1983; Hsu and Schulaw, 1984; Jacobson and Kollias, 1984; Warren et al., 1984; Mech et al., 1985). It has been reported recently that the effects of xylazine could be reversed by the indolealkylamine alkaloid, yohimbine HCl. Yohimbine HCl has been used to reverse xylazine HCl or xylazine HCl–ketamine HCl in white-tailed deer (Hsu and Schulaw, 1984; Mech et al., 1985), mule deer (*O. hemionus* Rafinesque) (Jessup et al., 1983) as well as several zoo animals (Jacobson and Kollias, 1984) and domestic species

(Hatch et al., 1982; Kitzman et al., 1982; Kitzman et al., 1984).

Xylazine HCl can also be reversed by another alpha$_2$-adrenergic antagonist, tolazoline HCl (2-benzyl-2-imidazoline). Tolazoline HCl has been used to antagonize xylazine HCl in domestic sheep (Toutain et al., 1982; Zingoni et al., 1982), cattle (Roming, 1984; Ruckebusch and Toutain, 1984), dogs (Tranquilli et al., 1984), mice and chickens (Hsu, 1981). This paper reports the use of tolazoline HCl to antagonize a xylazine HCl–ketamine HCl immobilization of white-tailed deer.

MATERIALS AND METHODS

This study was conducted from December 1984 through April 1985 in northern Minnesota. Fourteen adult deer (10 females, four males) were housed individually, fed commercial deer pellets of varying energy and protein content, and provided water ad libitum. In addition, 17 free-ranging deer were caught either by clover traps or rocket nets.

Every 14 days, all penned deer were immobilized with an initial dose of 100 mg xylazine HCl (Rompun®, Haver-Lockhart Laboratories, Shawnee, Kansas 66201, USA) (mean = 1.58 mg/kg; range = 1.09–2.27 mg/kg) and 300 mg ketamine HCl (Ketaset®, Bristol Laboratories, Syracuse, New York 13201, USA) (mean = 4.75 mg/kg; range = 3.27–6.82 mg/kg) administered intramuscularly (i.m.) via pole syringe. All deer were kept immobilized in left lateral recumbency with supplemental i.m. injections of ketamine HCl ranging from 200 to 900 mg to obtain blood and urine samples. After samples were collected, each deer was injected intravenously (i.v.) with tolazoline HCl (Sigma Chemical Co., St. Louis, Missouri 63178, USA). Tolazoline HCl was prepared just prior to use by dissolving it in sterile 0.9% sodium chloride solution to a concentration of 20 mg/ml. Doses of 0.25, 0.50, 1.0, 2.0 and 4.0 mg/kg were tested to determine the most efficacious dose. Arousal time (AT) and walk time (WT) were recorded. AT was the time from tolazoline HCl injection to when the animal opened its eyes and raised its head; WT was the time from tolazoline HCl injection to when the deer was able to walk. Auscultated heart rates and respiratory rates were recorded only on those penned deer receiving the two highest doses (15 deer, 18 trials). Six penned deer were given the initial xylazine HCl–ketamine HCl dose and allowed to re-

cover without reversal to act as controls. The free-ranging deer were subjected to the same immobilization protocol (i.m. injection with either pole or hand syringe), but tolazoline HCl was given only at the 2.0 and 4.0 mg/kg concentration.

Statistical analysis was by one- and two-way analysis of variance. Means are reported with standard deviations.

RESULTS

The results are based on 91 immobilizations and 85 reversals. There were 69 immobilizations of penned deer and 22 of free-ranging deer. Of the free-ranging deer, one was captured three times and three were captured twice. The induction time (interval between initial injection and immobilization) for the penned deer averaged 12.1 ± 4.3 min (range = 5–21 min). Induction times were not recorded for the free-ranging deer due to technician error. The total immobilization times for all deer ranged from 35 to 236 min.

Injection of 0.25 or 0.50 mg/kg tolazoline HCl had no apparent effect in four deer, so use of those concentrations was discontinued. The mean AT's for 1.0, 2.0, and 4.0 mg/kg tolazoline HCl were 8.2 ± 7.5, 5.9 ± 5.8, and 5.2 ± 4.6 min and mean WT's were 13.5 ± 8.4, 10.5 ± 8.6, and 9.2 ± 7.5 min (Table 1). The mean AT and WT for the control deer were 160.5 ± 48.0 and 168.2 ± 49.0 min. There was no significant difference in AT's or WT's among the three doses, between penned and free-ranging deer, or between male versus female ($P > 0.05$). There was also no significant difference in AT's or WT's between those deer receiving the minimum 200 mg ketamine HCl supplemental injection and those receiving the maximum amount required for continual immobilization ($P > 0.05$).

Heart rates increased significantly after tolazoline HCl administration at the 2.0 and 4.0 mg/kg doses ($P < 0.001$). The mean heart rate before and after giving 2.0 mg/kg tolazoline HCl was 42 ± 12 and 73 ± 19 beats/min. For the 4.0 mg/kg

TABLE 1.   Arousal and walk times of white-tailed deer immobilized with 100 mg xylazine HCl and 300 mg ketamine HCl then reversed with tolazoline HCl.

Tolazoline HCl dose (mg/kg)	Number of trials	Body weight (kg) Mean ± SD	Arousal time (min)		Walk time (min)	
			Mean ± SD	Range	Mean ± SD	Range
Control	6	57.9 ± 9.6	160.5 ± 48.0	98–234	168.2 ± 48.8	100–236
1.0	4	60.5 ± 5.3	8.2 ± 7.5	1–17	13.5 ± 8.4	2–21
2.0	57	65.3 ± 9.6	5.9 ± 5.8	1–27	10.5 ± 8.6	2–43
4.0	24	58.1 ± 8.4	5.2 ± 4.6	1–23	9.2 ± 7.5	2–35

dose, the before and after heart rates were 51 ± 12 and 93 ± 15 beats/min. There was no dosage effect of tolazoline HCl upon the degree of heart rate increase ($P > 0.05$).

There was no significant difference in respiratory rates after tolazoline HCl administration ($P > 0.05$). The respiratory rates before and after receiving 2.0 mg/kg tolazoline HCl were 45 ± 17 and 42 ± 15 breaths/min. The before and after respiratory rates for the 4.0 mg/kg dose were 48 ± 19 and 38 ± 17 breaths/min. The pattern of respiration changed quickly after tolazoline HCl injection. Although the rate dropped slightly, the deer went from shallow to deep thoracic breathing within a minute of injection.

DISCUSSION

Tolazoline HCl has been used for decades as a vasodilating agent in humans (Priscoline® HCl, CIBA Pharmaceutical Co., Summit, New Jersey 07901, USA) and its pharmacology is well documented (Ahlquist et al., 1947; Pieter et al., 1982; Ward, 1984). It has mixed receptor activity, being both a specific alpha$_2$-adrenergic antagonist as well as histamine$_2$ agonist (Sanders et al., 1975). This activity can result in tachycardia and cardiac arrhythmia in dogs (Lum and Nickerson, 1955) and increased gastric secretion and motility in humans (Ward, 1984). Such effects may not always be detrimental, however, Tolazoline HCl can control the bloating effect of xylazine HCl in sheep (Zingoni

et al., 1982). In our study, bloating occurred prior to tolazoline HCl reversal, but never after. Xylazine HCl also causes bradycardia in deer (Jessup et al., 1983; Hsu and Schulaw, 1984). The average heart rate for unanesthetized, standing deer during the same season as this study is about 75 beats/min (Moen, 1978). The heart rate for our drugged deer was 47 beats/min prior to reversal. Tolazoline HCl raised the mean heart rate to 83 beats/min and appeared to reverse the xylazine HCl-induced bradycardia in these deer.

No apparent adverse effects were noted in 85 trials with tolazoline HCl. After tolazoline HCl administration, the responses of the deer were quite similar. Once they were alert (head up, eyes opened), they usually raised their necks, rolled to a sternal position, and quickly stood. The deer would often walk with an uncertain gait which improved within a few minutes. Many deer appeared moderately sedated for a period after reversal, but capable of directed activity if stimulated. Some deer fed within 30 min after reversal. All deer were checked approximately every 15 min for 2–4 hr postreversal, then once daily thereafter.

The WT's for tolazoline HCL reversal compared favorably with those for yohimbine HCl (9.5 ± 10.4 min) used on these same deer subjected to a similar immobilization protocol (Mech et al., 1985). These reversal times are longer than when deer are immobilized with xylazine HCl

alone (4.4 ± 5.4 min) (Hsu and Schulaw, 1984). This could be due to these authors recording only times to standing but more likely it is due to our use of up to 900 mg ketamine HCl in the immobilization and handling procedure. This drug combination might also explain the range in response to tolazoline HCl (Table 1).

Both tolazoline HCl and yohimbine HCl are specific blockers of presynaptic alpha$_2$ adrenoceptors found in noradrenergic neurons. When stimulated by such drugs as xylazine HCl, these adrenoceptors decrease the turnover of norepinephrine in the spinal cord and the brain as well as decelerate its rate of synthesis. Tolazoline HCl and yohimbine HCl block this negative feedback and allow neural transmission to resume (Pieter et al., 1982).

The mode of action of ketamine HCl is still unknown. Hypotheses include a N-methylaspartate receptor- (Thomson et al., 1985) or sigma opioid receptor-mediated activity (Murray and Leid, 1984). Attempts to reverse ketamine HCl with yohimbine HCl in cats (0.25 mg/kg) have resulted in shortened arousal times but unchanged, or even extended, times to ambulation. Also, ketamine HCl catalepsy was not antagonized (Hatch and Ruch, 1974; Hatch et al., 1983). What might have occurred in our deer given a xylazine HCl–ketamine HCl mixture was that if the xylazine HCl was reversed before the various amounts of ketamine HCl were fully metabolized, the animal could have still have been under ketamine HCl influence and unable to recover fully. This could explain the range in AT's and WT's we observed.

Neither tolazoline HCl nor yohimbine HCl is without some adverse effects, but they appear negligible at this time. Yohimbine HCl is a more specific antagonist than tolazoline HCl (Pieter et al., 1982) and appears more potent on a milligram basis (Hsu, 1981). Tolazoline HCl, though, is much more soluble than yohimbine HCl. A maximum 5-mg/ml solution of yohim-

bine HCl is possible, whereas concentrations of 500 mg/ml tolazoline HCl are easily attainable. Thus, a sufficient dose of tolazoline can be administered in less than 1 ml. The costs of either drug are inconsequential, being less than $0.05/deer (U.S. currency).

Twice deer arose before tolazoline HCl was given i.v., so the deer were given the drug i.m. Although the complete recovery time for these deer was prolonged, they did not show signs of extended xylazine HCl sedation. In such cases of apparent premature recovery, it seems preferable to give tolazoline HCl i.m. rather than not at all.

Although there was no significant difference in WT's between the three doses, we subjectively felt that the 2.0- or 4.0-mg/kg doses of tolazoline HCl provided a quicker total recovery. We used the 2.0 mg/kg dose for the majority of reversals and feel this concentration to be satisfactory for most uses.

CONCLUSIONS

The use of 100 mg xylazine HCl and 300 mg ketamine HCl given i.m. is a more rapid and safer immobilization for healthy, adult white-tailed deer than xylazine alone (Hsu and Shulaw, 1984). Reversal with 2.0 or 4.0 mg/kg tolazoline HCl i.v. results in complete antagonism of drug effects. This combination provides for an effective, non-narcotic, inexpensive and reversible drug protocol for the immobilization of white-tailed deer.

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