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XYLAZINE HYDROCHLORIDE–KETAMINE HYDROCHLORIDE IMMOBILIZATION OF WOLVES AND ITS ANTAGONISM BY TOLAZOLINE HYDROCHLORIDE

Terry J. Kreeger,[1] Ulysses S. Seal,[2] and Alicia M. Faggella[3]

ABSTRACT: Fourteen wolves (*Canis lupus* L.) were singularly or repeatedly immobilized with 30 mg xylazine hydrochloride (HCl) and 400 mg ketamine HCl. Mean induction time was 5.3 ± 4.6 min (mean ± SD). Administration of 8.0 mg/kg tolazoline HCl as an antagonist significantly reduced immobilization times from 148.0 ± 52.7 to 47.9 ± 8.9 min ($F = 63.69$, df = 1,17, $P < 0.05$). The average times from injection to ambulation for 2.0, 4.0, and 8.0 mg/kg tolazoline HCl were 35.2 ± 31.8, 18.5 ± 11.7, and 10.2 ± 9.1 min. Tolazoline HCl increased heart rates significantly ($P < 0.001$) from 75 ± 14 to 120 ± 23 beats/min, reversing a xylazine HCl-induced bradycardia. Respiratory rates also increased significantly ($P < 0.01$) after tolazoline HCl injection from 19 ± 7 to 28 ± 8 breaths/min. Immobilization resulted in an initial hypertension which was normalized after tolazoline HCl administration. One female wolf had a single sinoatrial block within 1 min of receiving tolazoline HCl. Tolazoline HCl appears to be an effective antagonist for xylazine HCl–ketamine HCl immobilization of wolves.

INTRODUCTION

The combination of the alpha$_2$-adrenergic agonist, xylazine HCl, and the cyclohexane, ketamine HCl, has been used to immobilize numerous wild and domestic carnivores (Stephenson et al., 1978; Knight, 1980; Hebert and McFetridge, 1981; Parry et al., 1981; Nielson et al., 1982; Herbst et al., 1985). These drugs usually result in a smooth induction and recovery (Harthoorn, 1976) with the pressor and cataleptic effects of ketamine HCl being ameliorated by the depressor, sedative and myorelaxing effects of xylazine HCl (Amend, 1972). One drawback of this combination, however, is the extended recovery or prolonged sedation attributed to xylazine HCl (Parry et al., 1981; Hatch et al., 1982).

Tolazoline HCl is an alpha$_2$-adrenergic antagonist used to reverse xylazine HCl in domestic sheep (Toutain et al., 1982; Zingoni et al., 1982), cattle (Romig, 1984; Ruckebusch and Toutain, 1984), dogs (Tranquilli et al., 1984) and white-tailed deer (*Odocoileus virginianus*) Kreeger et al., 1986). This paper reports the use of tolazoline HCl to antagonize a xylazine HCl–ketamine HCl immobilization of gray wolves.

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MATERIALS AND METHODS

This study was conducted from January through March 1985 in south-central Minnesota. The husbandry of the test animals has been reported previously (Seal et al., 1979). Four captive wolves (two females, two males) were immobilized every 7 days with 30 mg xylazine HCl (Rompun®, Haver-Lockhart Laboratories, Shawnee, Kansas 66201, USA) and 400 mg ketamine HCl (Ketaset®, Bristol Laboratories, Syracuse, New York 13201, USA) administered intramuscularly (i.m.) via a gas-operated dart pistol or pole syringe. Each wolf would then receive either 2.0, 4.0 or 8.0 mg/kg tolazoline HCl (Sigma Chemical Co., St. Louis, Missouri 63178, USA) or 5 ml physiological saline administered intravenously (i.v.). This procedure continued weekly until all animals received all four treatments. The time from tolazoline HCl injection to when the animal was able to walk in a directed manner of its own accord was recorded (walk time = WT). Once an effective

TABLE 1. Walk times of wolves immobilized with 30 mg xylazine HCl and 400 mg ketamine HCl and then reversed with tolazoline HCl.

Tolazoline HCl dose (mg/kg)	Number of trials	Body weight (kg)	Walk time (min)		Total immobilization time (min)	
		Mean ± SD	Mean ± SD	Range	Mean ± SD	Range
Control	4	33.7 ± 3.6	115.0 ± 52.6	70–173	148.0 ± 52.7	103–206
2.0	4	33.7 ± 3.6	35.2 ± 31.8*	11–82	59.0 ± 21.4*	41–90
4.0	4	33.7 ± 3.6	18.5 ± 11.7*	9–34	52.5 ± 11.1*	37–61
8.0	16	33.1 ± 6.7	10.2 ± 9.1*	1–32	47.9 ± 8.9*	38–66

* Significantly different from control at $P < 0.05$.

dose was established based on WT's and absence of any adverse effects, 10 additional wolves (four females, six males) were similarly immobilized, processed and reversed. Auscultated heart rates and respiratory rates were recorded on all wolves receiving this selected dose. Test animals were observed intermittently for several hours post reversal.

In addition, two undrugged wolves (one female, one male) were transported to the University of Minnesota College of Veterinary Medicine to determine the effects of immobilization and reversal on cardiovascular parameters. These wolves were raised by humans and could be manually restrained for attachment of ECG electrodes (Datascope 871 Monitor, Datascope Corp., Paramus, New Jersey 07652, USA) and blood pressure cuff (Dynamap® Research Monitor, Critikon, Inc., Tampa, Florida 33607, USA). They were immobilized and reversed as before, with ECG and blood pressure recorded during induction and recovery.

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

RESULTS

The results are based on 28 immobilizations and 24 reversals. The mean xylazine HCl dose was 0.9 ± 0.2 mg/kg (range = 0.7–1.2 mg/kg); the mean ketamine HCl dose was 12.4 ± 2.5 mg/kg (range = 8.9–16.1 mg/kg). The induction time (interval between initial injection and immobilization) averaged 5.3 ± 4.6 min (range = 1.0–24.0 min). The time from induction to injection of tolazoline HCl averaged 32.9 ± 9.8 min. Immobilization times (time from immobilization to ambulation) ranged from 38 to 206 min with times for wolves receiving tolazoline HCl being significantly less than controls ($P < 0.05$) (Table 1).

The mean WT's for 2.0, 4.0, and 8.0 mg/kg tolazoline HCl were 35.2 ± 31.8, 18.5 ± 11.7, and 10.2 ± 9.1 min, respectively (Table 1). The mean WT for the control wolves was 115.0 ± 52.6 min. The only significant difference in WT's among the three doses was 2.0 versus 8.0 mg/kg ($P < 0.01$). The WT's for all three doses were significantly different than the control WT ($P < 0.05$).

Based on the above WT's, a dose of 8.0 mg/kg was selected. The heart rate significantly increased after tolazoline HCl administration from a mean of 75 ± 14 to 120 ± 23 beats/min ($P < 0.01$). Respiratory rates also increased significantly from a mean of 19 ± 7 to 28 ± 8 breaths/min ($P < 0.01$).

Administration of xylazine HCl–ketamine HCl caused an increase in blood pressure in the two wolves tested. The mean arterial blood pressure (MABP) rose from 106 torr (mean of both wolves) prior to immobilization to a maximum of 174 torr within 10 min of xylazine HCl–ketamine HCl injection. MABP initially decreased after tolazoline HCl administration, then rose steadily (Fig. 1). No arrhythmias were noted in the male; a single sinoatrial block was noted 1 min after tolazine HCl injection in the female.

DISCUSSION

Xylazine HCl is a specific alpha$_2$-adrenergic agonist (Doxey and Roach, 1980;

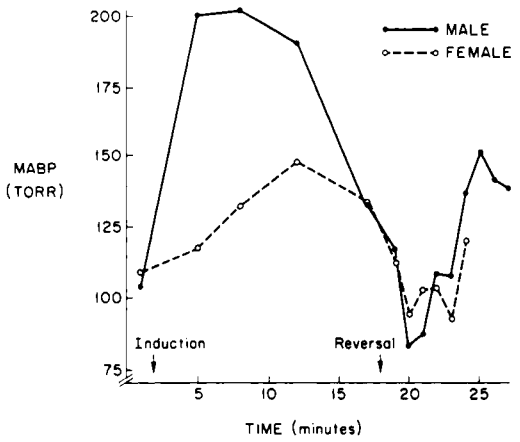

FIGURE 1. Mean arterial blood pressure (MABP) of two wolves immobilized with xylazine HCl–ketamine HCl and then reversed with tolazoline HCl.

Docherty and Stark, 1981), but may have other receptor or synaptic mechanisms which influence its actions (Anden et al., 1970; Delbarre and Schmitt, 1974; Audigier et al., 1976; Maggi et al., 1980; Hamburg and Tallman, 1981; Langer, 1981). The mechanism of action for ketamine HCl is still unknown. Investigations have implicated cholinergic (Authier et al., 1972), serotonergic (Hatch, 1973), dopamnergic, muscarinic, nicotinic cholinoceptive (Hatch and Ruch, 1974), *N*-methylaspartate (Thomson et al., 1985), or sigma opioid receptors (Murray and Leid, 1984). Tolazoline HCl has been used for decades in human medicine as a vasodilator or as a reversal agent for clonidine, another alpha$_2$-adrenergic agonist (Ahlquist et al., 1947; Pieter et al., 1982; Ward, 1984). It is both an alpha$_2$-adrenergic antagonist as well as a histamine$_2$ agonist (Sanders et al., 1975).

Xylazine HCl causes sedation and analgesia by stimulating central presynaptic alpha$_2$-adrenoceptors (Timmermans et al., 1981) which inhibit norepinephrine release from adrenergic nerve terminals (Starke, 1977; Hsu, 1981). Tolazoline HCl blocks or antagonizes this effect and restores neural transmission (Pieter et al., 1982).

Tolazoline HCl may only partially antagonize the effects of ketamine HCl. Supportive evidence for this comes from another alpha$_2$-adrenergic antagonist, yohimbine HCl (0.25 mg/kg), which was used on domestic cats given ketamine HCl (20 mg/kg). These cats demonstrated shortened arousal times, but catalepsy and ambulation times were not reversed or shortened (Hatch and Ruch, 1974; Hatch et al., 1983). Others have indicated that yohimbine HCl may have only a general stimulatory effect to override ketamine HCl (Hatch et al., 1983; Hsu and Lu, 1984).

We chose WT's as an end point to this experiment because even though the wolves sometimes raised their heads fairly quickly after tolazoline HCl administration, they did not appear to be "cerebrally aroused." They appeared to still be under partial influence of ketamine HCl with such signs as mydriasis, hyperpytalism and catalepsy. Full recovery, therefore, is probably a function of xylazine HCl reversal plus endogenous metabolism of ketamine HCl.

Another reason for measuring only WT was that the pattern of recovery was not consistent. Some animals after reversal would open their eyes and raise their heads, but recovered no further for some period; others would remain prostrate after injection, then quickly become sternal and stand. In all cases, however, recovery was characterized by initial head and neck, then forequarter, and lastly, hindquarter activation. There was no sign of prolonged sedation after reversal nor were any adverse effects noted.

Xylazine HCl causes bradycardia in dogs by either increasing vagal tone (Antonaccio et al., 1973), by decreasing sympathetic activity (Klide et al., 1975), or by responding to transient hypertension (Clark et al., 1982). The resting heart rate of an unanesthetized wolf is unknown, but for the domestic dog the rate is between 100 and 130 beats/min (Swanson, 1977).

Tolazoline HCl, which causes tachycardia in unanesthetized animals (Ward, 1984), raised the mean heart rate from 75 ± 14 to 120 ± 23 beats/min, thus reversing the xylazine-induced bradycardia in wolves.

Tolazoline HCl caused premature ventricular contractions in dogs anesthetized with thiopental sodium and cyclopropane (Lum and Nickerson, 1956). The only arrhythmia noted in this study was a single sinoatrial block in the female wolf 1 min after tolazoline HCl injection. The cause or significance of this is unknown. Unfortunately, only a few wolves were available for this portion of the study. Further investigations of tolazoline HCl effect on cardiovascular parameters need to be conducted.

Xylazine HCl has caused hypertension followed by hypotension in dogs (Hsu et al., 1985). Blood pressures of the two wolves also appeared to follow this trend (Fig. 1). The hypertensive effect of xylazine HCl is probably due to activation of vascular alpha-adrenoceptors, whereas the hypotensive effect has been attributed to decreased sympathetic activation (Hsu et al., 1985). The initial hypotension after tolazoline HCl administration could be due to the continuing fall in blood pressure induced by the as yet unreversed xylazine HCl. It could also be due to the vasodilator properties of tolazoline HCl. Tolazoline HCl given i.v. produces vasodilation and cardiac stimulation with blood pressure responding to the relative contributions of each. The net effect is usually pressor (Goodman, 1980).

Tolazoline HCl increased the respiratory rate, but did not change the pattern in wolves. In white-tailed deer given tolazoline HCl, the pattern went from shallow, abdominal to deep, thoracic incursions, but the rate did not change (Kreeger et al., 1986). Yohimbine HCl increased ventilation in dogs (Luckens and Malone, 1973), so the effect of tolazoline HCl was not unexpected. It is unknown why tolazoline HCl affects the respiratory pattern of wolves differently than deer.

Another difference between wolves and deer was in the relative amount of tolazoline HCl required to achieve reversal of xylazine HCl. Deer immobilized with 100 mg xylazine HCl and varying amounts of ketamine HCl had WT's of 10.5 ± 8.6 min when given 2.0 mg/kg tolazine HCl (Kreeger et al., 1986). Wolves given 30 mg xylazine HCl required 8.0 mg/kg tolazoline HCl to achieve similar WT's (10.2 ± 9.1 min). The total amount of tolazoline HCl averaged 116 mg for the deer and 268 mg for the wolves. These responses could be due to differences in receptor populations or peripheral metabolism of the drug.

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