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CARDIOVASCULAR AND BEHAVIORAL RESPONSES OF GRAY WOLVES TO KETAMINE-XYLAZINE IMMOBILIZATION AND ANTAGONISM BY YOHIMBINE

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ABSTRACT: Adult wolves (*Canis lupus*) were immobilized with 6.6 mg/kg ketamine hydrochloride (KET) and 2.2 mg/kg xylazine hydrochloride (XYL) administered intramuscularly. Induction time was 4.6 ± 0.3 min ($\bar{x}$ ± SE). Immobilization resulted in significant bradycardia and hypertension ($P < 0.05$). Twenty min after induction, the wolves were given 0.05–0.60 mg/kg yohimbine hydrochloride (YOH). Yohimbine given intravenously produced dose-related increases in heart rate (HR) with doses >0.15 mg/kg resulting in extreme tachycardia (>300 bpm). All doses of YOH caused a temporary decrease in mean arterial blood pressure (MABP) with some individual animals manifesting profound hypotension (<30 torr) at doses >0.15 mg/kg. Increasing the dose of YOH above 0.15 mg/kg did not significantly decrease either arousal or ambulation times. Administering YOH at 40 or 60 min after induction resulted in decreased arousal and ambulation times. Stimulation by weighing and taking repeated blood samples during anesthesia did not shorten arousal times. We recommend that wolves immobilized with XYL-KET be antagonized with doses of YOH <0.15 mg/kg.

Key words: Blood pressure, *Canis lupus*, heart rate, ketamine, wolves, xylazine, yohimbine, chemical immobilization.

INTRODUCTION

Use of YOH to antagonize KET and/or XYL immobilization of wild species has increased substantially in recent years (Jessup et al., 1983; Hsu and Schulaw, 1984; Jacobson and Kollias, 1984; Jacobson et al., 1985; Jessup et al., 1985; Mech et al., 1985; Ramsay et al., 1985; Renecker and Olson, 1985; Kreeger and Seal, 1986a, b). Due to the nature of these studies, a thorough investigation of the physiological effects of these drugs has not been feasible. None of these drugs used individually, or in combination, are without adverse effects. Ketamine can cause convulsions, catalepsy, hyperreflexia, hypertension, tachycardia, and cardiac arrhythmias (White et al., 1982). Xylazine can induce respiratory depression, hypotension, bradycardia, and cardiac arrhythmias (Antonaccio et al., 1973; Klide et al., 1975; Hatch et al., 1982). Yohimbine has been reported to cause hyper- and hypotension, tachycardia, cardiac arrhythmias, and behavioral changes (Sanghvi and Gershon, 1970; Hatch, 1973; Hatch and Ruch, 1974; Goldberg and Robertson, 1983).

The purpose of this study was to examine the cardiovascular and behavioral responses of wolves to XYL-KET immobilization with antagonism by YOH under controlled conditions.

MATERIALS AND METHODS

This study was conducted from January through June 1986 in east-central Minnesota. Eleven adult wolves (4 females, 7 males) weighing from 24 to 42 kg were used at different times for the various experiments. The wolves were housed in groups of two in outdoor, cement runs with kennel boxes. The animals were fed commercial dry dog food supplemented with road-killed white-tailed deer (*Odocoileus virginianus*) and provided water ad libitum. All wolves

were vaccinated for rabies, distemper, parvovirus, hepatitis, and leptospirosis. None had heartworm (*Dirofilaria immitis*).

The wolves were immobilized with 6.6 mg/kg KET (Ketaset®, Bristol Laboratories, Syracuse, New York 13201, USA) and 2.2 mg/kg XYL (Rompun®, Haver-Lockhart Laboratories, Shawnee, Kansas 66201, USA) given together intramuscularly via pole or hand-held syringe. Yohimbine (Sigma Chemical Co., St. Louis, Missouri 63178, USA) was administered in the cephalic vein. Yohimbine was dissolved in sterile, distilled water with mild heating (<50 C) then diluted with 50% dextrose solution to yield a 5% dextrose solution containing 5 mg/ml YOH. Placebo-treated animals received intravenous injections of 5% dextrose.

Experiment I

Five wolves (1 female, 4 males) were immobilized every 7–14 days. Upon induction, each animal was quickly transported indoors, placed in lateral recumbency, and fitted with electrocardiogram (ECG) electrodes in lead II configuration (Datascope 871 Monitor, Datascope Corp., Paramus, New Jersey 07652, USA) and an oscillometric blood pressure cuff (Dinamap® Research Monitor, Critikon, Inc., Tampa, Florida 33607, USA). Electrocardiograms and mean arterial blood pressure (MABP) were recorded every minute for the first 5 min then every 5 min thereafter until administration of YOH. Just prior to antagonism, each animal was muzzled. Exactly 20 min after induction, the animals were given either 0.05, 0.10, 0.15, 0.20, 0.30, 0.40, 0.50, 0.60 mg/kg YOH or a comparable volume of 5% dextrose. This procedure continued until all wolves received all doses in a Latin Squares design. Electrocardiograms and MABP were recorded every minute after YOH administration for 15 min or until the animal tried to stand. The HR and MABP recorded during the first minute of immobilization after the wolves were brought indoors were not significantly different than those of undrugged wolves (Kreeger et al., 1986). Therefore, values recorded during this first minute were presumed to be close to "normal" and characterization of cardiac function (bradycardic, hypotensive, etc.) were related to these induction values.

Experiment II

After completion of Experiment I, six wolves (2 females, 4 males) were similarly immobilized and given the same doses of YOH in the same experimental design. In a single blind paradigm, the individual injecting YOH or placebo determined the head up time (HUT) and walk time (WT) without knowing which animal received which dose. Head up time was the time from injection of YOH or placebo to when the animal initially raised its head from lateral recumbency. Walk time was the time from injection of YOH or placebo to when the animal could walk in a directed, coordinated manner as well as recognize and respond appropriately to objects, other wolves, and humans.

Experiment III

Yohimbine does not completely antagonize KET in wolves (Kreeger and Seal, 1986b). Moreover, decreasing the amount of KET relative to XYL reduced WT after YOH administration (Kreeger et al., unpubl. data). To determine if complete recovery in wolves anesthetized with KET-XYL could be a function of endogenous metabolism of KET after antagonism of XYL by YOH, all 11 wolves were immobilized as before, then given 0.10 mg/kg YOH at either 20, 40, or 60 min after induction. This procedure continued at a minimum 7 day interval until all wolves were treated at each time interval. Head up time and WT were recorded only for wolves remaining immobilized for the prescribed periods.

Experiment IV

In all previous experiments, external stimulation of the anesthetized wolves was minimized. Since this is not the case in field situations, anesthetized wolves were stimulated to determine if this would decrease the immobilization period. The six wolves used in Experiment II were immobilized as before and brought indoors. Each was stimulated by weighing and taking blood samples from the cephalic vein every 10 min until HUT. This time was chosen as the end point since arousal in the field would dictate that either additional drugs were required or further manipulation of the animal should be abandoned. HUT's in this experiment were compared to the HUT's in Experiment II.

Statistical analyses were with ANOVA. Statistical significance was determined at $P < 0.05$. Means are reported with standard errors (SE).

RESULTS

Experiment I

The mean induction time ($n = 45$) was 4.6 ± 0.3 min. HR decreased after induction (min 1) to become significantly bradycardic at 10–20 min ($P < 0.01$). MABP became hypertensive at 3–20 min ($P < 0.04$) (Fig. 1). Injection of placebo at 20

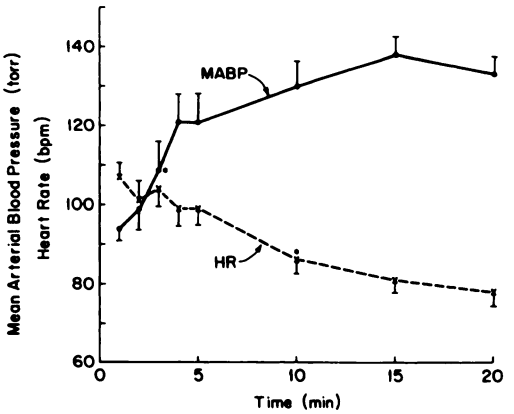

FIGURE 1. Heart rates (bpm) and mean arterial blood pressures (torr) of wolves during immobilization by KET-XYL. *Point in time at which values become significantly different from values at min 1 ($P < 0.05$).

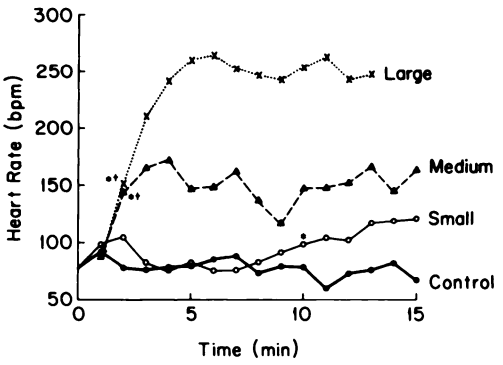

FIGURE 2. Heart rates of wolves immobilized with KET-XYL then given increasing doses of YOH at 20 min postinduction (time 0). Small = mean heart rate of 0.05 and 0.10 mg/kg doses of YOH; Medium = 0.15 mg/kg dose of YOH only; Large = mean of 0.2–0.6 mg/kg doses of YOH. Standard errors have been omitted for simplicity. *Point in time at which values become significantly different from control values ($P < 0.05$). †Point in time at which values become significantly different from Small values ($P < 0.05$).

min did not change HR or MABP. The wolves remained bradycardic and hypertensive for the remainder of the test. One male wolf had recorded intermittent premature ventricular contractions (PVC) during immobilization. No other arrhythmias were recorded.

Injection of small doses of YOH (0.05 and 0.10 mg/kg) increased HR above control values at 10 min and above induction values at 13 min postadministration ($P < 0.05$) (Fig. 2). Injection of 0.15 mg/kg YOH (medium dose) caused a more rapid increase in HR which was greater than either control or induction values at 2–15 min ($P < 0.05$) (Fig. 2). Administration of 0.20–0.60 mg/kg YOH caused a marked tachycardia (Fig. 2). The HR for these five doses were not different from each other at any time post YOH ($P = 0.26$). No recordings were made at 14 and 15 min because wolves given these large doses were uncontrollable by this time. HR resulting from these doses were more rapid than control, induction and the small doses at 2–13 min post YOH ($P < 0.01$) and more rapid than HR recorded with the 0.15 mg/kg YOH dose at 5–13 min ($P < 0.03$) (Fig. 2).

At some time during recovery, every wolf given 0.20–0.60 mg/kg YOH had HR >300 bpm. The most rapid HR was 369 bpm recorded at 5 min postinjection for a male wolf given 0.20 mg/kg YOH. No wolf given either 0.05 or 0.10 mg/kg YOH had HR >200 bpm. No cardiac arrhythmias were recorded after administration of YOH. Yohimbine also abolished the PVC recorded for the one wolf during immobilization.

All doses of YOH decreased MABP relative to control values (Fig. 3). There were no differences in MABP among doses within either the small dose or the large dose groups ($P = 0.47$). The lowest single MABP recorded was 21 torr (28/14, systolic/diastolic) for the same wolf that had the most rapid HR. This hypotension developed concurrently with the tachycardia.

Experiment II

Head up times and WT for all doses of YOH were shorter than controls ($P < 0.01$) (Fig. 4). The HUT for 0.05 mg/kg YOH was longer than for 0.15–0.60 mg/kg ($P < 0.01$). The HUT for 0.10 mg/kg was longer than for 0.20–0.60 mg/kg ($P < 0.03$). The HUT for 0.15 mg/kg was longer than that

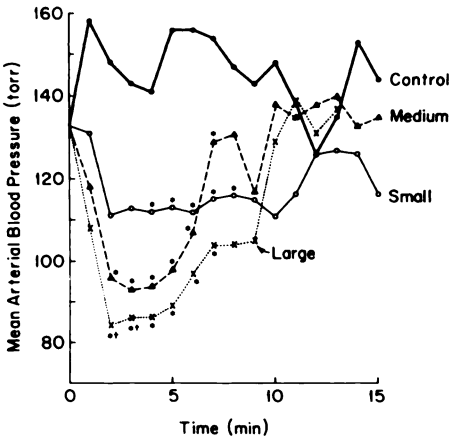

FIGURE 3. Mean arterial blood pressures of wolves immobilized with KET-XYL then given increasing doses of YOH at 20 min postinduction (time 0). Categories and analyses same as in Figure 2.

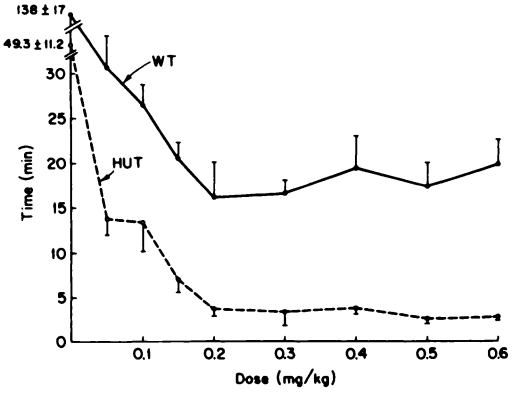

FIGURE 4. Head up (HUT) and walk times (WT) of wolves immobilized with KET-XYL then given increasing doses of YOH. See text for analyses.

of the 0.40–0.60 mg/kg doses ($P < 0.05$). There was no difference in HUT among the 0.20–0.60 mg/kg doses ($P = 0.86$).

The WT for 0.05 mg/kg was longer than for 0.15–0.60 mg/kg ($P < 0.05$). The WT for 0.10 mg/kg was longer than those for 0.20, 0.30, and 0.50 mg/kg ($P < 0.05$). There was no difference between WT for the 0.15–0.60 mg/kg doses ($P = 0.58$).

There were no differences between the sexes in HUT or WT at any dose ($P = 0.55$). In general, wolves given doses >0.20 mg/kg had more difficult recoveries characterized by ataxia, hyperreflexia, and hypersalivation.

Experiment III

Of the 11 wolves used in this experiment, all remained immobilized for 20 min, eight for 40 min, and only two for 60 min. Comparisons were made between groups of only those wolves which remained immobilized for each period. HUT and WT decreased as length of immobilization increased (Table 1).

Experiment IV

The HUT for wolves given a variety of stimulations was 59.8 ± 10.2 min. This was not different than the control HUT in Experiment II of 61.0 ± 10.0 min ($P = 0.52$).

DISCUSSION

Experiment I

Xylazine is a non-selective alpha-adrenergic agonist (Anden, 1970; Audigier et al., 1976; Doxey and Roach, 1980; Maggi et al., 1980). Dogs sedated with XYL develop a transient hypertension followed by a prolonged hypotension and bradycardia (Klide et al., 1975). The initial hypertension could be produced by XYL acting on extrasynaptic, alpha$_2$-adrenoceptors located in vascular smooth muscle resulting in vasoconstriction (Langer, 1981). The subsequent hypotension and bradycardia are thought to be mediated by pre- and postsynaptic alpha$_2$-adrenoceptors in the hindbrain which decrease central sympathetic outflow and increase vagal tone (Antonaccio et al., 1973; Cavero and Roach, 1980; Hucht et al., 1981; Langer, 1981; McCall et al., 1983).

Ketamine increases heart rate, blood pressure, and cardiac output probably by direct stimulation of central receptors to increase sympathetic and decrease parasympathetic outflow (Chodoff, 1972; Stanley, 1973; Wong and Jenkins, 1974; Folts et al., 1975; Clark et al., 1982). Several

receptor types have been implicated as sites of action for KET including cholinergic, serotonergic, dopaminergic, opioid, and N-methyl-aspartic (Finck and Ngai, 1982; White et al., 1982; Anis et al., 1983; Leeuwin et al., 1984).

In this experiment, XYL and KET were administered simultaneously which resulted in eventual bradycardia and hypertension (Fig. 1). These results were in agreement with similar studies on dogs (Clark et al., 1982; Kolata and Rawlings, 1982). The positive chronotropic and hypertensive effects of KET may have attenuated the bradycardic and hypotensive properties of XYL in this study.

Yohimbine is considered an alpha$_2$-adrenergic antagonist, but it may interact with opioid, cholinergic, serotonergic, or dopaminergic receptors as well (Sanghvi and Gershon, 1970; Zetler and Thorner, 1973; Scatton et al., 1980; Goldberg and Robertson, 1983). Yohimbine acts as follows: norepinephrine (NE), released in the synaptic cleft by an action potential, reaches a threshold concentration which activates presynaptic alpha$_2$-adrenoceptors which serve to inhibit the further release of NE. Xylazine acts as an agonist at these presynaptic adrenoceptors to inhibit NE release, while YOH antagonizes this negative feedback to increase the release of NE (Langer, 1981). The sedative and cardiovascular effects of XYL are all mediated by alpha adrenoceptors which can be antagonized by YOH (Goldberg and Robertson, 1983). Yohimbine may partially antagonize the effects of KET either by blocking a subset of common receptors or by acting as a general nervous system stimulant (Hsu and Lu, 1984; Kreeger and Seal, 1986b). In support of this, YOH (0.20 mg/kg) significantly shortened HUT for wolves immobilized only with KET (25.0 mg/kg), but WT did not differ from controls (Kreeger and Seal, 1986b). Similar findings were reported for domestic cats (Hatch et al., 1983).

TABLE 1. Head up, walk, and total immobilization times of wolves immobilized with KET-XYL then given 0.10 mg/kg YOH at three different times after onset of anesthesia.

Time yohimbine given (min)	*n*	Head up time (min)	Walk time (min)	Total immobilization time (min)
20	8	12.9 ± 2.6	29.6 ± 3.2	49.6 ± 3.2
40	8	5.9 ± 1.6[a]	19.6 ± 4.9	60.9 ± 9.6
60	2	1.5 ± 0.5[a]	5.5 ± 0.5[a]	65.5 ± 0.2[a]

[a] Values significantly different from values at 20 min at $P < 0.05$.

Yohimbine has minimal direct cardiac effects which consist only of small increases in HR (Gomes et al., 1980). Centrally, YOH could increase HR by directly antagonizing the bradycardic properties of XYL, or at high doses, by enhancing a positive chronotropic response to nerve stimulation by increasing NE release (Lokhandwala and Buckley, 1976; Yamaguchi et al., 1977; Langer, 1981).

In this experiment, the low doses of YOH increased HR at 10 min postinjection indicating partial XYL antagonism with probable expression of the positive chronotropic effects of KET. The tachycardia developed at 0.15–0.60 mg/kg YOH could be a function of central XYL antagonism coupled with the central positive chronotropic effects of both KET and YOH.

One purpose of testing YOH at 0.10 mg/kg increments beyond 0.20 mg/kg was to identify a level at which cardiac arrhythmias began to appear. Doses of YOH greater than 0.125 mg/kg caused cardiac disturbances in dogs with arrhythmias developing at 0.5 mg/kg (Hatch et al., 1982). No arrhythmias were recorded at any time for any dose of YOH in this study. Xylazine sedation, or XYL-KET immobilization, can also cause arrhythmias in dogs such as sino-atrial block, sino-atrial arrest, primary and secondary atrio-ventricular block, PVC, and sinus tachycardia (An-

tonaccio et al., 1973; Clark et al., 1982). In this study, only one wolf had sporadic PVC while immobilized with XYL-KET.

The initial decrease in MABP recorded at all doses of YOH could be due to a direct action on extrasynaptic alpha$_2$-adrenoceptors in vascular smooth muscle resulting in vasodilation (Drew, 1976; Doxey et al., 1978). As YOH reaches the CNS, the central hypotensive properties of XYL could be antagonized allowing the pressor effects of KET to again predominate.

Extreme tachycardia results in decreased cardiac output and hypotension (Miller, 1981). A decrease in cardiac output secondary to YOH-induced tachycardia and possible direct YOH-induced vasodilation could account for the severe hypotension recorded in some animals. Although no animals died, complete cardiovascular collapse is possible in a compromised animal unable to compensate for such hypotension.

Experiment II

The purpose of this experiment was to determine if increasing the dose of YOH would decrease the HUT and WT of wolves immobilized with XYL-KET. Doses of YOH greater than 0.10 mg/kg did not shorten the WT, indicating that for this immobilization protocol a threshold for YOH probably exists beyond which additional drug does not increase antagonism efficacy. Thresholds for YOH have been suggested for white-tailed deer (Mech et al., 1985).

Experiment III

Walk times decreased as immobilization times increased. This supports the hypothesis that complete antagonism of XYL-KET immobilization could be a function of XYL antagonism by YOH and endogenous biotransformation of KET to inactive metabolites. These findings imply that the more KET a wolf is given, the longer the recovery time will be after YOH is administered.

Experiment IV

Although we found that the immobilization dose was satisfactory, we were concerned that the decreased amount of KET compared to previous experience would result in only a "lightly anesthetized" animal. The results of this experiment show that the immobilization dose used provides a working time of approximately 20–40 min in an unexcited wolf. However, a wolf that was subjected to prolonged pursuit or physiological stress would be expected to have a shorter immobilization time or require a larger initial immobilizing dose.

Conclusions

Based on the significant cardiovascular responses and the relative nonsignificant differences in HUT and WT, we recommend that wolves immobilized with XYL-KET be antagonized with doses of YOH less than 0.15 mg/kg.

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