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Source: Journal of Wildlife Diseases, 25(1) : 89-94

Published By: Wildlife Disease Association

URL: https://doi.org/10.7589/0090-3558-25.1.89

Journal of Wildlife Diseases, 25(1), 1989, pp. 89–94

PHYSIOLOGICAL RESPONSE OF GRAY WOLVES TO BUTORPHANOL–XYLAZINE IMMOBILIZATION AND ANTAGONISM BY NALOXONE AND YOHIMBINE

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ABSTRACT: Captive gray wolves (*Canis lupus*) were immobilized (loss of consciousness) with 2.0 mg/kg xylazine hydrochloride (XYL) and 0.4 mg/kg butorphanol tartrate (BUT) administered intramuscularly. Induction time was 11.8 ± 0.8 min (mean ± SE). Immobilization resulted in bradycardia, respiratory depression, and normotension. Fifteen min after induction, six wolves were given either 0.05 mg/kg naloxone hydrochloride (NAL) and 0.125 or 0.250 mg/kg yohimbine hydrochloride (YOH), or an equal volume of saline (control) intravenously. Antagonism resulted in shortened recovery times compared to control animals ($P < 0.03$); there was no difference in recovery times between the YOH doses ($P > 0.05$). Antagonism caused increases in heart rate (HR) and respiratory rate (RR), but no changes in MABP. Eight other wolves were similarly immobilized, but given only NAL. This resulted in partial antagonism with the animals appearing to be sedated with XYL only. Three wolves given only 0.4 mg/kg BUT assumed a state described as "apathetic sedation." Three other wolves sedated with only 2.0 mg/kg XYL showed a profound sedation characterized by recumbency, bradycardia and shallow, but regular, respiration. This study demonstrated that (1) BUT and XYL together, but not separately, can completely immobilize wolves, (2) this combination can be rapidly antagonized by NAL and YOH, and (3) there appeared to be no adverse cardiopulmonary reactions to any of the drugs used.

Key words: Wolves, *Canis lupus*, heart rate, blood pressure, respiration, butorphanol, xylazine, naloxone, yohimbine, chemical immobilization, experimental study.

INTRODUCTION

Gray wolves (*Canis lupus*) have been immobilized with a variety of drugs or drug combinations including ketamine hydrochloride (KET) (Kreeger and Seal, 1986), KET and promazine hydrochloride (Seal and Mech, 1983), KET and xylazine hydrochloride (XYL) (Kreeger et al., 1987), and etorphine hydrochloride (Fuller and Keith, 1981). There are advantages and disadvantages with these drugs. Xylazine and etorphine can be antagonized with yohimbine hydrochloride (YOH) and diprenorphine, respectively (Fuller and Keith, 1981; Kreeger et al., 1987), but etorphine is a controlled substance and potentially lethal to humans should accidental injection occur (Parker and Haigh, 1982). Ketamine is not a controlled drug, but currently no antagonist exists (Kreeger and Seal, 1986).

Butorphanol tartrate (BUT) is a synthetic agonist-antagonist morphinan analogue with a potency of 3.5 to 7 times that of morphine in humans and horses (Kalpravidh et al., 1984). As a class, agonist-antagonist properties vary with dose and affected receptor population (Rosow, 1986). Butorphanol is thought to be a mu receptor antagonist (Pircio et al., 1976) as well as a kappa and sigma receptor agonist (Rosow, 1985). Butorphanol probably acts as a competitive antagonist at the mu receptor, but produces analgesic effects by agonist activity at kappa receptors (Rosow, 1985). Butorphanol is not a controlled substance. Its primary uses in veterinary medicine are as an analgesic in horses (Gingerich et al., 1985) and as an antitussive agent in small animals (Cavanagh et al., 1976). In dogs, BUT produces minimal cardiovascular and respiratory effects, minimal sedation, but good analgesia (Pircio et al., 1976).

Xylazine is primarily an alpha-adrenergic agonist, but may have other receptor activity as well (Anden et al., 1970; Del-

barre and Schmitt, 1974; Audigier, 1976; Maggi et al., 1980). Xylazine can cause profound sedation, but not immobilization (here defined as loss of consciousness), in wolves (Philo, 1978). Xylazine sedation is characterized by hypotension, bradycardia, respiratory depression and analgesia (Klide et al., 1975; Booth, 1982).

The purpose of this study was to examine (1) efficacy of BUT and XYL for immobilizing wolves, (2) antagonism of that immobilization by naloxone hydrochloride (NAL) and YOH, and (3) the physiological responses of wolves to these drugs.

MATERIALS AND METHODS

This study was conducted in June 1987. The locality and husbandry of the captive wolves have been previously described (Kreeger et al., 1987). Drugs and dosages used were 0.4 mg/kg BUT (Bristol Laboratories, Syracuse, New York 13221, USA) and/or 2.0 mg/kg XYL (Rompun, Haver-Lockhart Laboratories, Shawnee, Kansas 66201, USA) administered intramuscularly (i.m.) via pole or hand-held syringe. Antagonists used were 0.05 mg/kg NAL and either 0.125 or 0.250 mg/kg YOH (Sigma Chemical Co., St. Louis, Missouri 63178, USA) administered via the cephalic vein. Naloxone was prepared by dissolving it in physiological saline to a concentration of 10.0 mg/ml. Preparation of YOH has been previously reported (Kreeger et al., 1987). The control substance was comparable volumes of physiological saline. Some wolves were also given 0.02 mg/kg atropine sulfate i.m. (Fort Dodge Laboratories, Inc., Fort Dodge, Iowa 50501, USA). All experiments were conducted 7 days apart.

Experiment one

Six adult wolves (three female, three male) were immobilized with BUT and XYL. Upon induction (loss of consciousness), 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, mean arterial blood pressure (MABP), and respiratory rate (RR) were recorded at 5 min intervals for the first 15 min after induction and at 1 min intervals for 10 min after antagonism or until the animal tried to stand. After 15 min of immobilization, each wolf received one of three treatments: (1) NAL plus 0.125 mg/kg YOH, (2) NAL plus 0.250 mg/kg YOH, (3) physiological saline. There were two wolves in each treatment group per week for 3 wk. Thus, every wolf received each treatment while serving as its own control. Head-up times (HUT) and walk times (WT) were also measured for all replications. Head-up time was from injection of the antagonist until the animal raised its head from lateral recumbency; WT was from injection of the antagonist until the animal could walk in a directed, coordinated manner.

Experiment two

The same six animals used in Experiment one were anesthetized as before, but not given an antagonist. Instead, atropine was administered i.m. 15 min postinduction to determine its chronotropic and inotropic effects. Electrocardiograms, MABP, and RR were measured at 1 min intervals for 5 min after injection.

Experiment three

Eight different adult wolves (three females, five males) were anesthetized as before, but were given only NAL 15 min after induction as an antagonist. This was done to determine if the BUT component of the drug combination used was reversible by NAL.

Experiment four

Three male wolves were given 0.4 mg/kg BUT i.m. with no antagonist and analyzed for their reaction to this drug alone.

Experiment five

One female and two male wolves were given only 2.0 mg/kg XYL i.m. and their response to this drug was also assessed.

Statistical analyses were by one- and two-way ANOVA and Fisher's Least Significant Difference test (Number Cruncher Statistical Systems, Kaysville, Utah 84037, USA). Statistical significance was determined at $P \leq 0.05$. Means are reported with standard errors (SE).

RESULTS

Experiment one

Wolves given BUT/XYL were recumbent in 4.4 ± 0.3 min, but did not become fully immobilized until 11.8 ± 0.8 min after injection. At 5 min postinduction, heart rate was 43.4 ± 3.2 beats per minute (bpm) and did not vary throughout im-

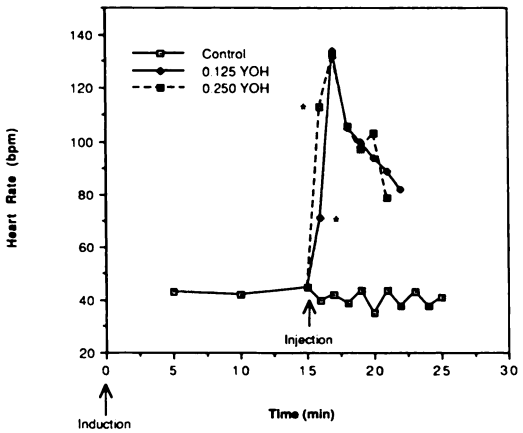

FIGURE 1. Mean heart rates of wolves immobilized with butorphanol and xylazine and injected with one of two doses of yohimbine or saline 15 min postinduction. Standard errors have been omitted for simplicity. *Point at which values become significantly different from control values.

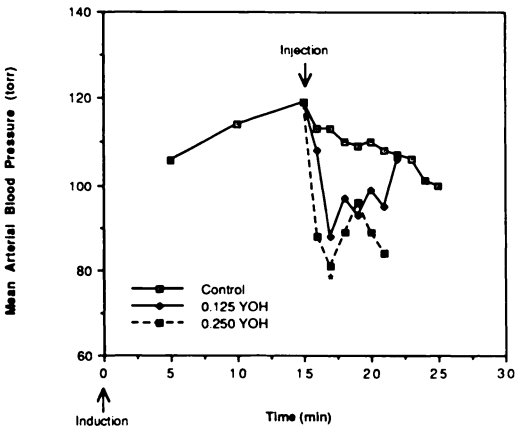

FIGURE 2. Mean arterial blood pressure response of wolves immobilized with butorphanol and xylazine and injected with one of two doses of yohimbine or saline 15 min postinduction. Standard errors have been omitted for simplicity. *Significantly different from control value.

mobilization ($P = 0.55$; Fig. 1). Blood pressure showed a slight but non-significant increase during immobilization ($P = 0.26$; Fig. 2). Respiratory rate was 8.3 ± 1.0 respirations per minute (rpm) within 5 min of induction and also did not vary throughout immobilization ($P = 0.55$; Fig. 3).

Ten min after saline injection, the control animals showed no significant changes in HR, MABP, or RR ($P > 0.05$). One min after administration of NAL and either YOH dose, HR increased significantly compared to control values ($P < 0.001$), peaked by the second minute, then slowly decreased (Fig. 1). Except for the first minute, HR did not differ between the two YOH doses ($P > 0.05$). Administration of NAL and either YOH dose lowered MABP although this differed from control values ($P < 0.006$) only at 2 min after injection of the 0.250 mg/kg dose of YOH (Fig. 2). There were no differences in MABP between the two YOH doses ($P > 0.05$).

Respiratory rate increased 2 min after injection of the antagonists and remained elevated thereafter. There were no differences in RR between the two YOH doses ($P > 0.05$). Respiratory rate increased over control RR after 5 min at the lower dose of YOH ($P < 0.05$) and by the second minute at the higher dose of YOH ($P < 0.05$).

There was no difference in the HUT (3.8 ± 1.2 versus 4.0 ± 1.5 min) and WT (5.0 ± 0.9 versus 4.8 ± 1.2 min) between the two YOH doses ($P = 0.94$). Both doses resulted in significantly shortened recoveries compared to control HUT (39.4 ± 13.4 min) and WT (40.8 ± 13.5 min) ($P < 0.03$). Arousals tended to be fast and often with-

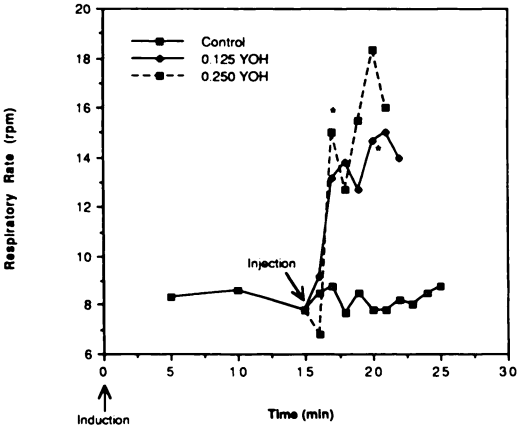

FIGURE 3. Mean respiratory rate of wolves immobilized with butorphanol and xylazine and injected with one of two doses of yohimbine or saline 15 min postinduction. Standard errors have been omitted for simplicity. *Point at which values become significantly different from control values.

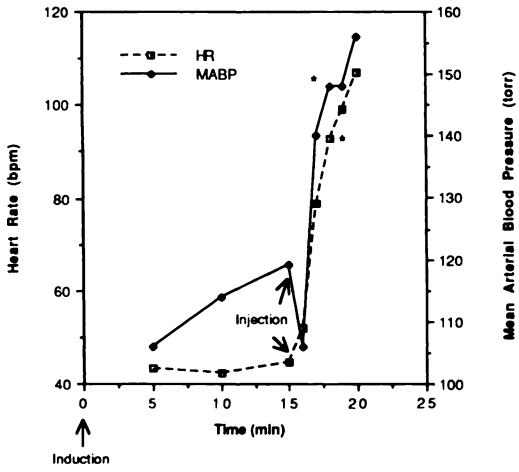

FIGURE 4. Mean heart rate and arterial blood pressure of wolves immobilized with butorphanol and xylazine and injected with atropine. Standard errors have been omitted for simplicity. *Point at which values become significantly different from control values.

out preliminary indication. Return to complete normalcy was judged to occur within 5 min of WT.

Experiment two

Immobilized wolves given atropine showed increases in both HR and MABP within 3 min of injection ($P < 0.02$; Fig. 4). Respiratory rate also increased slightly, but not significantly ($P > 0.05$).

Experiment three

Wolves immobilized with BUT/XYL, but antagonized only with NAL, showed signs similar to XYL sedation; they could be aroused when stimulated, but returned quickly to a profoundly sedated state (see Results, Experiment five).

Experiment four

Animals given only BUT became sedate in 18.0 ± 1.2 min of administration. The animals appeared calm and seemingly disinterested in their surroundings and their eyes were characterized by blepharophimosis. However, noises or nearby motion would elicit arousal. Return to normalcy was judged to be 166.3 ± 34.8 min.

Experiment five

Wolves receiving XYL only became profoundly sedate in 9.0 ± 1.5 min. Thirty min after injection, auscultated HR was 40.0 ± 1.2 bpm and RR was 20.0 ± 2.3 rpm. Sedation was characterized by sternal recumbency, eyes closed, and regular but shallow, respiration. Loud noises would generally elicit arousal, but reversion to sedation was rapid after the stimulus ceased. Recovery to a subjectively determined normal state was 128.0 ± 10.5 min.

DISCUSSION

Experiment one

Although using BUT in dogs produced minimal cardiovascular and respiratory changes (Pircio et al., 1976), it did not appear to protect against the bradycardic and respiratory depressant effects of XYL (Booth, 1982). The HR and RR of undrugged, sleeping wolves measured by radiotelemetry were 54.0 ± 5.0 bpm and 19.1 ± 4.0 rpm, respectively (Kreeger, unpubl. data). Blood pressure, however, was fairly consistent and at no time in the experiment was it either hypo- or hypertensive relative to the MABP of undrugged wolves (Kreeger et al., 1986).

Of interest was the apparent failure of 0.250 mg/kg YOH to elicit the profound tachycardia (>300 bpm) recorded in wolves anesthetized with XYL and KET (Kreeger et al., 1987). Low doses of YOH are thought to have minimal cardiac effects consisting of small increases in HR (Gomes et al., 1980). Higher doses of YOH could enhance a positive chronotropic response to nerve stimulation by increasing norepinephrine release (Langer, 1981). Ketamine has positive chronotropic effects (Folts et al., 1975). Thus, it appears that YOH produced a synergistic effect with KET to cause tachycardia at YOH doses >0.15 mg/kg. The caveat to administer YOH doses below this level (Kreeger et al., 1987) does not apply to wolves immobilized with XYL and BUT.

Experiment two

Administration of atropine resulted in a rapid increase in HR accompanied by an increase in MABP. Atropine markedly reduces or abolishes the cardiac inhibitory effect of xylazine (Adams, 1982). Although cardiovascular function appeared adequate in this study, atropine could be administered to ameliorate the adverse effects of XYL if desired. It should be noted, however, that the relative hypertension and tachycardia produced by atropine could be undesirable as it increases myocardial oxygen consumption that may increase the potential for arrhythmias.

Experiment three

The purpose of this experiment was to determine if NAL could antagonize the BUT component of the BUT/XYL immobilizing combination. Wolves receiving NAL alone appeared to react as if they were sedated with XYL only. The animals could be aroused if stimulated, but quickly resumed a posture and attitude similar to XYL sedation. Naloxone probably antagonizes all classes of opioid receptors (Rosow, 1985) and appeared to antagonize the effects of BUT.

Experiment four

In humans, BUT produces a state termed "apathetic sedation" where patients appear quite sleepy, yet remain responsive (Martin et al., 1976). This description might well be applied to the wolves given BUT. The level of sedation produced by BUT was demonstrably less than that produced by XYL and was insufficient to allow handling of the animals.

Experiment five

Wolves given XYL alone were heavily sedated, but not immobilized. A variety of manipulations can be performed on wolves sedated only with XYL (Philo, 1978; Kreeger et al., 1988), yet complete immobilization (i.e., loss of consciousness) apparently requires the synergistic central nervous system sedative effects of BUT or other drugs.

CONCLUSIONS

We concluded that (1) the BUT/XYL combination was capable of immobilizing captive wolves, (2) NAL and YOH quickly and effectively antagonized this immobilization, and (3) there appeared to be no adverse cardiopulmonary responses to any of the drugs. Currently, we feel that the BUT/XYL combination would best be used for captive or trapped animals. Its efficacy on free-ranging or highly excited animals was not tested. The major advantages of this drug combination were that (1) immobilization could be produced using small volumes (<2.5 ml), (2) immobilization could be rapidly and completely antagonized, and (3) none of the drugs used were controlled substances. These experiments also suggested that the use of the agonist/antagonist class of synthetic opioids could have potential application in wildlife immobilization due to their efficacy, reversability and relative safety for both humans and animals.

ACKNOWLEDGMENTS

We would like to thank Bristol Laboratories for the donation of butorphanol; L. David Mech for his review of this manuscript; the U.S. Fish and Wildlife Service for the use of the wolves; the Minnesota Department of Natural Resources for the use of their facilities; and the College of Veterinary Medicine, University of Minnesota, for the use of the equipment used in this study. This work was supported by the Veteran's Administration Medical Center, Minneapolis, Minnesota.

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Received for publication 26 January 1988.