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Source: Journal of Wildlife Diseases, 23(4) : 619-624

Published By: Wildlife Disease Association

URL: https://doi.org/10.7589/0090-3558-23.4.619

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Journal of Wildlife Diseases, 23(4), 1987, pp. 619–624
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IMMOBILIZATION OF WHITE-TAILED DEER BY ETORPHINE AND XYLAZINE AND ITS ANTAGONISM BY NALMEFENE AND YOHIMBINE

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ABSTRACT: White-tailed deer (*Odocoileus virginianus*) were immobilized with either 4.0 mg etorphine hydrochloride (ETOR) or 3.5 mg ETOR and 50.0 mg xylazine (XYL). Deer immobilized with ETOR only were given 4.0 mg nalmefene hydrochloride (NAL), a new opioid antagonist, 20 min after induction. Deer immobilized with ETOR and XYL received 3.5 mg NAL and 0.125 mg/kg yohimbine hydrochloride (YOH). The dose of 4.0 mg ETOR did not provide acceptable immobilization and was discontinued. A NAL:ETOR ratio of 1:1 was insufficient for complete and sustained antagonism of ETOR. Subsequently, deer were immobilized with ETOR and XYL as before which was then antagonized with 35.0 mg NAL and 0.125 mg/kg YOH. The 10:1 ratio of NAL:ETOR appeared to provide complete antagonism with no evidence of renarcotization. Although more study is required, NAL could become a useful antagonist for opioid-induced immobilizations.

Key words: White-tailed deer, *Odocoileus virginianus*, etorphine hydrochloride, xylazine, nalmefene, yohimbine hydrochloride, chemical immobilization, antagonist.

INTRODUCTION

Etorphine hydrochloride (ETOR) and/or xylazine hydrochloride (XYL) have been used previously to immobilize white-tailed deer (*Odocoileus virginianus*) (Woolf, 1970; Presnell et al., 1973; Hsu and Shulaw, 1984). The effects of ETOR can be antagonized by diprenorphine hydrochloride (Woolf, 1970) or naloxone hydrochloride (Haigh, 1982). The effects of XYL can be antagonized by yohimbine hydrochloride (YOH) (Hsu and Shulaw, 1984). Both opioid antagonists have disadvantages, however. Diprenorphine has purported agonistic qualities (Hall and Clarke, 1983). Naloxone has a short half-life which could result in renarcotization (Fishman et al., 1973; Ngai et al., 1976; Haigh, 1982; Aitkinhead, 1984).

Nalmefene (NAL) (17-(cyclopropylmethyl)-4,5a-epoxy-6-methylenemorphinan-3,14-diol) is a recently-developed, pure narcotic antagonist structurally similar to naloxone and having a therapeutic index of approximately 5,000 (Dixon et al., 1986). Depending on the species, NAL is from 16 to 28 times more potent than naloxone (Dixon et al., 1986). The duration of action of NAL in humans is much longer than naloxone (Gal and Difazio, 1985).

Because of its potency, lack of agonistic properties, and possible duration of action, NAL could be a useful antagonist for opioid-induced immobilization of wildlife. The purpose of this study, therefore, was to determine if NAL could effectively antagonize immobilization by ETOR of captive white-tailed deer.

MATERIALS AND METHODS

This study took place in September 1986 in Marshfield, Wisconsin. The average daily temperature was 13 C. A total of 15 captive adult deer (five female, 10 male) was used. Body weights ranged from 58 to 95 kg. The deer were kept in a 0.32-ha pen with access to inside shelter. The deer were fed commercial deer pellets and alfalfa hay and provided water ad libitum. Food was withheld 24 hr prior to experimentation. The experiments were conducted at the same time in the morning, 2 wk apart. The experimental design randomized animals within treatment and within dates. All animals were monitored hourly on the day of the experiment and daily thereafter. All deer were immobilized with drugs delivered by gas-powered pistol or .22 caliber-powered rifle.

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Statistical analyses were with one-way ANOVA (Number Cruncher Statistical Systems, Kaysville, Utah 84037, USA). Statistical significance was determined at $P \leq 0.05$. Means are reported with standard errors.

Group 1

Initially, three male deer were immobilized by intramuscular (i.m.) injection of 4.0 mg ETOR (0.05–0.07 mg/kg) (M99, Lemmon Company, Rockville, Maryland 20850, USA). Exactly 20.0 min after induction (lateral recumbency), these deer received 4.0 mg nalmefene hydrochloride (NAL) (0.05–0.07 mg/kg) (Schering Research, Miami, Florida 33137, USA) via the jugular vein. Nalmefene was prepared by dissolving it in sterile 0.9% NaCl to a concentration of 10.0 mg/ml. Head-up times (HUT) and walk times (WT) were recorded on all deer for all trials. Head-up time was the time from injection of NAL to when the deer raised its head from lateral recumbency; WT was the time from injection of NAL to when the deer stood and walked on its own, but not necessarily assessed to be completely normal.

Group 2

Because of unacceptable immobilizations obtained with Group 1, subsequent trials were conducted. Six deer (three females, three males) were immobilized with 3.5 mg ETOR (0.04–0.06 mg/kg) and 50.0 mg XYL (0.5–0.8 mg/kg) (Rompun, Haver-Lockhart, Cutter Laboratories Inc., Shawnee, Kansas 66201, USA) delivered as before. Twenty min after induction, these animals received 3.5 mg NAL (0.04–0.06 mg/kg) and 0.125 mg/kg YOH (Sigma Chemical Co., St. Louis, Missouri 63178, USA) intravenously (i.v.) in separate syringes. Preparation of YOH was previously reported (Kreeger and Seal, 1986).

Group 3

Another group of four deer (two females, two males) were immobilized with 3.5 mg ETOR (0.04–0.05 mg/kg) and 50.0 mg XYL (0.6–0.8 mg/kg) as before then given 35.0 mg NAL (0.4–0.5 mg/kg) and 0.125 mg/kg YOH i.v. 20.0 min after induction.

Group 4

Since Groups 2 and 3 required a combination of drugs to achieve adequate immobilization, three male deer (one from Group 1) were given 50.0 mg XYL (0.5–0.7 mg/kg) to determine the effects of XYL alone versus the effects of XYL plus ETOR. These animals were given 0.125 mg/kg YOH i.v. only 20.0 min after induction.

Group 5

Control animals consisted of the four deer that were used in Group 3. Each received 3.5 mg ETOR (0.04–0.06 mg/kg) and 50.0 mg XYL (0.5–0.8 mg/kg), but were given only 0.125 mg/kg YOH i.v. 20.0 min after induction. Animals that did not recover by 2 hr following YOH administration were given 35.0 mg NAL i.v. to prevent possible complications of extended immobilization.

RESULTS

Group 1

Inductions of the three deer given ETOR only were characterized by hyperactivity (constant pacing), hyperpnea and ataxia. One of these deer remained hyperactive for 31.0 min after receiving ETOR i.m. in the hindlimb musculature with no indication of imminent immobilization and was given 50.0 mg XYL i.m. Induction was achieved 3.0 min after this injection. Twenty min postinduction, this deer received 4.0 mg NAL and 0.125 mg/kg YOH i.v. and was standing in less than 1.0 min after administration. For the next hour this animal was alert, but paced continuously with open-mouthed breathing. Two and one-half hr after antagonism, the animal appeared sedated and could be touched by a human, but would not allow a rectal temperature to be taken. About 9 hr after antagonism, it was found dead. Histopathological examination conducted at the University of Minnesota (Department of Pathobiology, College of Veterinary Medicine, St. Paul, Minnesota 55108, USA) revealed severe congestion of the lungs and myocardial congestion and hemorrhage. These lesions supported a diagnosis of hyperthermia (Spraker, 1982).

The other two animals were successfully immobilized with induction times of 15.0 and 19.0 min. Both had HUT <1.0 min and WT of 1.0 min after being given 4.0 mg NAL (Table 1). Recovery for one deer was characterized by alertness, hyperactivity, and hyperpnea for 2 hr postantagonism. Approximately 9 hr after receiving

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TABLE 1. Recovery times and behavior after antagonism of white-tailed deer immobilized with etorphine or etorphine/xylazine then given either nalmefene or nalmefene/yohimbine.

		Immobilization		Antagonism				
Group	Sex[a]	ETOR (mg)	XYL (mg)	NAL (mg)	YOH (mg)	HUT[b] (min)	WT[c] (min)	Behavior after antagonism[d]
1	M	4.0	0.0	4.0	0.0	0.5	1.0	1, 2, 3
1	M	4.0	50.0[e]	4.0	7.5	0.5	1.0	1, 2, 4, 6
1	M	4.0	0.0	4.0	0.0	0.5	1.0	1, 2, 4, 6
2	F	3.5	50.0	3.5	7.2	5.0	32.0	4
2	F	3.5	50.0	3.5	7.6	1.0	2.0	4, 7
2	F	3.5	50.0	3.5	8.0	0.5	1.0	4, 5
2	M	3.5	50.0	3.5	8.1	1.0	2.0	4, 5
2	M	3.5	50.0	3.5	11.5	1.0	2.0	3, 4
2	M	3.5	50.0	3.5	10.6	4.0	5.0	1, 2, 3
3	F	3.5	50.0	35.0	5.4	0.5	1.0	7
3	F	3.5	50.0	35.0	5.6	1.0	2.0	7
3	M	3.5	50.0	35.0	9.0	2.0	3.0	7
3	M	3.5	50.0	35.0	8.0	1.0	2.0	7
4	M	0.0	50.0	0.0	9.0	na[f]	na	7
4	M	0.0	50.0	0.0	11.8	1.0	14.0	4
4	M	0.0	50.0	0.0	11.0	na	na	7
5	F	3.5	50.0	0.0	5.4	2.0	25.0	2, 3
5	F	3.5	50.0	0.0	5.6	2.0	122.0	4
5	M	3.5	50.0	0.0	8.0	120.0	121.0	4
5	M	3.5	50.0	0.0	9.0	6.0	86.0	2, 3

[a] M, male; F, female.
[b] Head-up time.
[c] Walk time.
[d] Behavioral codes: 1, hyperactive; 2, hyperpnea; 3, ataxic; 4, sedate; 5, unusual posture or gate; 6, died; 7, normal.
[e] Induction not achieved with etorphine alone.
[f] Deer standing on own when antagonist given.

NAL, this animal displayed an unusual hopping gait, but appeared to be breathing normally. The recovery of the other animal was also characterized by alertness, hyperactivity, and hyperpnea. This behavior continued for several hours. About 10 hr postantagonism, the animal appeared sedated with its mouth open, ears laid back, and eyes half closed. Approximately 22 hr after antagonism, it was extremely sedate, but could not be manually restrained to allow its temperature to be taken and 15.0 mg NAL was administered i.m. Two hr later this animal was found dead. Gross pathology was unremarkable. Histopathological examination revealed only moderate renal congestion and there was no confirmed diagnosis. The induction times and behavior of these animals were not considered acceptable.

Group 2

Because of the poor induction achieved with Group 1, the immobilization protocol was changed to ETOR and XYL with antagonism by NAL and YOH. Induction time for all deer receiving this combination (Groups 2 and 3) was 15.7 ± 2.0 min. Head-up time was 2.1 ± 0.8 min and WT was 7.3 ± 5.0 min. There was no difference between sexes in any of these parameters (P = 0.16, 0.50 and 0.11, respectively). Walk time, but not HUT (P = 0.22), was significantly shorter than in control animals ($P < 0.003$) (Table 1).

Although all deer responded immediately to NAL and YOH, they remained moderately to severely sedated for several hours after antagonism. Other behaviors noted shortly after antagonism were pac-

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ing, hyperpnea, ataxia, vocalization, and circling (Table 1).

Group 3

The HUT for these four deer was 1.1 ± 0.3 min and the WT was 2.0 ± 0.4 min. Again, HUT was not different from controls ($P = 0.32$), but WT was shorter ($P < 0.009$). All of the deer in this group appeared alert after antagonism. Two were found lying sternally about 20.0 min after antagonism, but rose and walked away quickly and steadily when approached by a human. All of these deer appeared normal 24 hr after antagonism.

Group 4

Induction time for the three deer receiving just XYL was 12.7 ± 7.2 min. Two deer were standing on their own 20.0 min after induction, but were sedate enough to be easily approached and given an i.v. injection of YOH. The remaining animal had a HUT of 1.0 min and a WT of 24.0 min after receiving YOH. One of these deer appeared moderately sedated after YOH; the other two deer remained alert and coordinated. Other abnormal behavior was not observed after antagonism with YOH.

Group 5

Induction time for control animals was 16.5 ± 4.7 min which was not different than the induction time for Groups 2 and 3 ($P = 0.83$). Head-up time was 32.5 ± 29.2 min; WT was 88.5 ± 22.8 min. Two of the deer stood <2 hr after administration of YOH, but would not remain standing and were extremely ataxic (Table 1). All deer received 35.0 mg NAL i.v. approximately 2 hr after receiving YOH. All became alert and coordinated within 2.0 min after administration, but two deer displayed hyperpnea and vocalization after receiving NAL.

DISCUSSION

Group 1

Immobilization of captive white-tailed deer with 4.0 mg ETOR should have been adequate (Woolf, 1970; Fowler, 1978), but this dose appeared to be insufficient to achieve consistent and acceptable induction times. None of these deer were considered highly excited or were pursued for lengthy periods prior to immobilization. Higher doses might have resulted in shorter induction times, but this is not supported by other studies (Woolf, 1970). Antagonism of 4.0 mg ETOR by 4.0 mg NAL appeared to provide incomplete antagonism because the hyperactivity and hyperpnea after antagonism were similar to behavior observed during induction. This prolonged activity could result in hyperthermia which may have been a major factor in the death of these animals. Although there are no pathognomonic characteristics of hyperthermia, the history and histopathological findings were suggestive that this was the cause of death (Spraker, 1982).

The initial 1:1 ratio of NAL:ETOR was chosen as a starting dose based on limited clinical data in humans. In human males, the highest useful dose of NAL for reversal of narcotic overdose was 1.0–2.0 mg i.v. (Dixon et al., 1986). Thus, the 4.0 mg dose of NAL seemed to be an appropriate starting dose for a different species and a different narcotic. However, it appeared that this dose only achieved transient antagonism since all animals seemed to revert to a partially narcotized state. This could be due to a shorter half-life in animals compared to humans. The half-life of NAL in horses is 0.8 hr compared to 8 to 9 hr in humans (Dixon, pers. comm.). The half-life of NAL in deer is unknown.

Group 2

The dosages of ETOR and XYL used in this study were greater than those previously reported, yet induction times were longer (Presnell et al., 1973). Again, a 1:1 ratio of NAL:ETOR was administered and all animals demonstrated behaviors after antagonism that were not observed when the deer were given higher doses of NAL

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(Group 3) or given only XYL and YOH (Group 4). The pacing and open-mouthed breathing appeared to be characteristics of ETOR narcotization.

Group 3

The most consistent and satisfactory recoveries from immobilization occurred in this group. The two deer that became sternally recumbent after antagonism could have been influenced by incomplete antagonism of XYL by YOH (see discussion, Group 4), but their response to approaching humans and overall attitude and behavior was judged to be normal. The 10:1 ratio of NAL:ETOR appeared to eliminate any effects attributable to ETOR narcotization.

Group 4

The 50.0 mg XYL dose was intended to control for the effects of XYL when used in combination with ETOR and not intended to immobilize these deer (Hsu and Shulaw, 1984). However, all three became laterally recumbent for at least a short period. The dose of 0.125 mg/kg YOH was chosen as this has been reported previously for ungulates (Jessup et al., 1983; Hsu and Shulaw, 1984). This dose, however, may have been too low because residual sedation occurred which was not observed in deer given higher doses of YOH (Mech et al., 1985). Nonetheless, none of these deer displayed behaviors such as hyperactivity and hyperpnea which appear to have been attributable to ETOR.

Group 5

Three of the four control deer raised their heads shortly after administration of YOH indicating partial antagonism of the drug combination. All of these deer required NAL to regain normalcy.

CONCLUSIONS

From the results of this study, we concluded the following:

(1) A 4.0 mg dose of ETOR was insufficient to provide satisfactory immobilization of the deer used in this study;
(2) Addition of 50.0 mg XYL to 3.5 mg ETOR provided complete, but not rapid immobilization;
(3) Nalmefene administered at a 1:1 ratio to ETOR provided immediate, but short-term antagonism of ETOR-induced immobilization;
(4) Nalmefene administered at a 10:1 ratio to ETOR provided immediate and lasting antagonism of ETOR-induced immobilization; and
(5) Based on the data from this limited study, we currently recommend that NAL be administered at a 10:1 ratio to ETOR when used on white-tailed deer.

ACKNOWLEDGMENTS

We are grateful to Schering Research, Miami, Florida, for providing the nalmefene used in this study. We would like also to thank Tim O'Brien, University of Minnesota College of Veterinary Medicine, for his assistance in the pathological examinations. This study was supported by the Marshfield Medical Foundation, Marshfield, Wisconsin, and the Veteran's Administration Medical Center, Minneapolis, Minnesota.

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Received for publication 10 February 1987.

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