EFFICACY AND SAFETY OF NALTREXONE HYDROCHLORIDE FOR ANTAGONIZING CARFENTANIL CITRATE IMMOBILIZATION IN CAPTIVE ROCKY MOUNTAIN ELK (CERVUS ELAPHUS NELSONI)

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EFFICACY AND SAFETY OF NALTREXONE HYDROCHLORIDE FOR ANTAGONIZING CARFENTANIL CITRATE IMMOBILIZATION IN CAPTIVE ROCKY MOUNTAIN ELK (*CERVUS ELAPHUS NELSONI*)

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ABSTRACT: We evaluated efficacy and safety of naltrexone for antagonizing carfentanil immobilization in 12 captive Rocky Mountain elk (*Cervus elaphus nelsoni*) using a randomized incomplete block experiment. In three replicate trials, elk were hand-injected with 10 μg carfentanil citrate/kg body weight intramuscularly. Fifteen min after each elk became recumbent, we administered naltrexone HCl (25% of dose intravenously, 75% subcutaneously) dosed at 0 (control), 25, 50, or 100 mg/mg carfentanil; after an additional 15 min of immobilization, controls received 500 mg naltrexone HCl/mg carfentanil. Elk were immobilized in 34 of 36 attempts; the mean (±SE) induction time was 3.1 ± 0.2 min. Regardless of dose, all elk stood <9 min after receiving naltrexone; controls remained immobilized until they received antagonist. Mean recovery times did not differ with increasing naltrexone dose ($P = 0.31$) or among individuals ($P = 0.16$). None of the elk receiving 100 or 500 mg naltrexone/mg carfentanil renarcotized, but three of eight and seven of nine elk receiving 50 and 25 mg naltrexone/mg carfentanil, respectively, showed signs of mild renarcotization 8 to 24 hr later ($P = 0.0002$). We observed no adverse clinical effects in elk receiving ≤500 mg naltrexone/mg carfentanil. Based on these data, we recommend 100 mg/mg carfentanil as a minimum effective dose for rapidly antagonizing immobilization and preventing renarcotization.

Key words: Naltrexone HCl, carfentanil citrate, Rocky Mountain elk, *Cervus elaphus nelsoni*, chemical immobilization, narcotic antagonist, experimental study.

INTRODUCTION

Powerful synthetic opiates are essential tools for capturing and handling wild ungulates. These drugs provide rapid induction and relatively long-lasting immobilization that can be completely reversed by specific opiate antagonists. Although wild ungulates initially recover within minutes of receiving an antagonist, some wild ungulates immobilized with synthetic opiates revert to a partially or completely narcotized state several hours later (Haigh, 1982; Franzmann and Lance, 1986). Factors believed to predispose or contribute to renarcotization include rapid metabolism of antagonists; deposition of opiates in fat, subcutaneous tissues, or fascial planes during injection; entero-hepatic shunting of opiates or metabolites; extremely high opiate doses; and variable individual or species sensitivities to opiates (Haigh, 1982; Franzmann and Lance, 1986). Renarcotization can potentially compromise survival of affected individuals and represents a shortcoming of opiate immobilization in wild ungulates.

Using long-acting opiate antagonists should prevent or minimize renarcotization in wild animals immobilized with synthetic opiates like carfentanil citrate. Unfortunately, the effective durations of most available antagonists appear too short to completely prevent renarcotization in large ungulates immobilized with carfentanil. Renarcotization has been observed with use of diprenorphine, nalmefene, or naloxone HCl to antagonize carfentanil (Jessup et al., 1985; Allen, 1989; Haigh, 1991).

Naltrexone HCl is a pure opiate antagonist with no agonist activities (Booth, 1988). Naltrexone HCl appears to offer significant advantages over other synthetic opiate antagonists studied to date. Naltrexone and its major active metabolite, 6-β-naltrexone, have much longer metabolic

half-lives than naloxone in humans (3.9 to 12.9 hr; Verberg, 1976; Crabtree, 1984); in dogs, however, duration is considerably shorter (Pace et al., 1979). Although metabolic half-live studies of naltrexone have not been reported in ungulates, there is evidence that duration of antagonist effects is sufficient to prevent renarcotization in several wild ungulate species (Schmitt and Dalton, 1987; Allen, 1989; Haigh, 1991). In this study, we evaluated efficacy and safety of varying doses of naltrexone HCl for antagonizing carfentanil citrate immobilization and preventing renarcotization over a 24-hr period in captive Rocky Mountain elk (*Cervus elaphus nelsoni*).

MATERIALS AND METHODS

We used 12 hand- and dam-raised captive Rocky Mountain elk maintained at the Colorado Division of Wildlife's Foothills Wildlife Research Facility (Fort Collins, Colorado, USA; 40°35′N, 105°10′W) in our experiment. Our experimental group included eight females and four castrated males that were 1.3- to 6.3-yr old and weighed 178 to 338 kg. Individual elk were identified by uniquely coded eartags. These elk were held with other nonstudy elk in three separate or interconnected pastures (each about 2 ha) before and between trials. Elk received ad libitum quantities of cubed alfalfa hay, long-stem grass hay, water, and mineralized salt blocks along with limited quantities of a pelleted supplement (Baker and Hobbs, 1985) throughout the study period.

Our study was designed as a randomized incomplete block experiment. We conducted replicate trials on 21 August, and 4 and 18 September, 1992, between 0600 and 1100. For each trial, we assigned elk to one of four naltrexone dose treatment groups receiving 0 (control), 25, 50, or 100 mg naltrexone HCl/mg carfentanil administered. Treatment assignments were random, except that individuals were only assigned to a dose treatment once.

Each elk was weighed (±0.5 kg) on a calibrated scale immediately prior to carfentanil administration during each trial. We then hand-injected carfentanil citrate (3 mg/ml; Wildnil®, Wildlife Pharmaceuticals, Incorporated, Fort Collins, Colorado), dosed at 10 μg/kg body weight, deep into the large muscle mass of the left hindquarter. Immediately after carfentanil administration, elk were released into individual isolation pens (about 50 m^2) for observation. We monitored pulse and respiration rates and rectal temperatures periodically to assure these parameters remained within acceptable limits. Elk received assigned naltrexone HCl doses (50 mg/ml; Investigational New Animal Drug 6277, Wildlife Pharmaceuticals, Incorporated) 15 min after they became recumbent; after an additional 15 min of immobilization, control elk received 500 mg naltrexone HCl/mg carfentanil. We injected 25% of the total naltrexone dose intravenously (IV) and 75% subcutaneously (SC); we divided antagonist doses in order to provide both immediate and prolonged systemic availability of naltrexone. Observers recorded induction times and responses to naltrexone at 1 min intervals for 16 min after administration; observers were not informed of naltrexone doses administered. All elk were observed from outside isolation pens, and we provided no prodding or other stimulation to encourage recovery.

Antagonist effects were evaluated using a qualitative scoring system (1 = no effect, 2 = increased respiration and muscular control, 3 = sternally recumbent with head erect, 4 = standing, 5 = normal mobility and attitude). We regarded standing as the most objective measure of recovery, and consequently equated standing with recovery in comparing dose responses. Because we recorded observations at 1 min intervals, many reported recovery times slightly (≤0.9 min) overestimated actual recovery.

We subsequently observed all elk at about 1, 8, 12, 24, 48, and 72 hr after immobilization for signs of renarcotization or other adverse effects. We defined renarcotization as any combination of abnormalities in the animal's behavior, appearance, approachability, gait, coordination, or level of consciousness attributable to narcotic agonism.

We compared mean recovery to standing times among naltrexone dose treatments by analysis of variance with dose, individual, trial, and dose by trial interactions as main effects using a computerized statistical program (PROC GLM; SAS Institute, Incorporated, 1988). We also compared renarcotization rates associated with varying naltrexone doses, as well as across trials, using Fisher's exact probability tests (Mielke and Berry, 1992).

RESULTS

Elk were immobilized with single intramuscular (IM) injections of carfentanil in 34 of 36 attempts; mean (±SE) induction time was 3.1 (±0.2) min. In trial 1, two adult cows were not completely immobi-

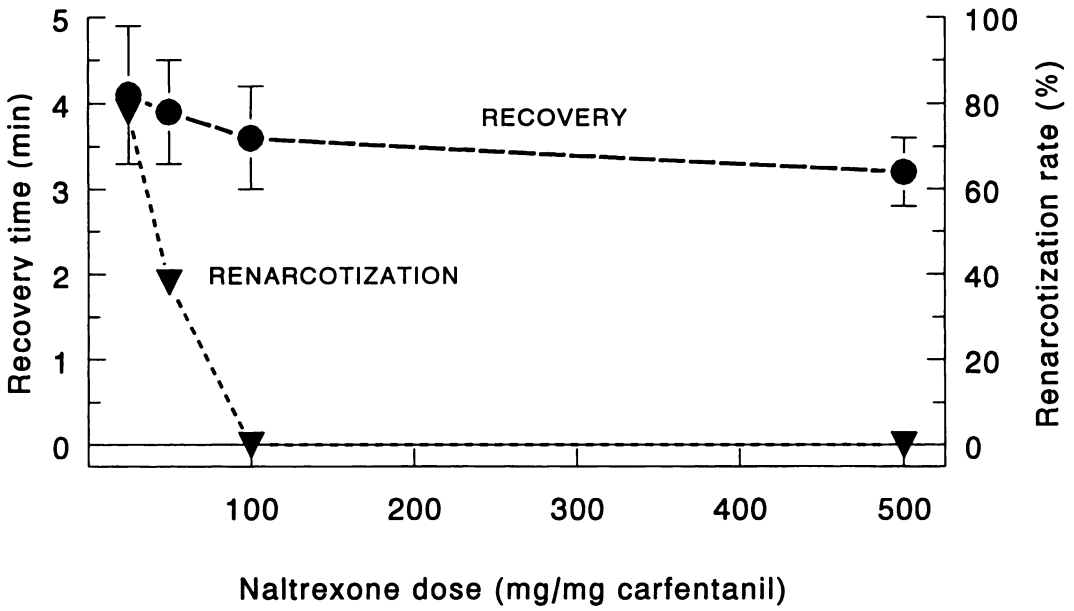

FIGURE 1. Although mean recovery times (●) of elk did not differ with increasing naltrexone doses (P = 0.68), renarcotization rates (▲) increased dramatically among elk receiving 50 or 25 mg naltrexone/mg carfentanil (P = 0.0002). Vertical bars represent ±1 SE of mean recovery times.

lized 30 min after receiving carfentanil, and consequently their data were not included in comparisons. Regardless of dose, all elk stood <9 min after receiving naltrexone, and 27 (79%) of 34 stood ≤4 min after receiving naltrexone; in contrast, control elk remained immobilized throughout the 15 min monitoring period prior to naltrexone administration. Mean recovery times did not differ with increasing naltrexone doses (P = 0.31) (Fig. 1) or among individuals (P = 0.16). Mean recovery times increased (P = 0.05) about 1.2 min over the three replicate trials, but we observed no dose by trial interaction (P = 0.36).

We observed no evidence of renarcotization in any of the elk receiving 100 or 500 mg naltrexone/mg carfentanil, but three of eight and seven of nine elk receiving 50 and 25 mg naltrexone/mg carfentanil, respectively, had signs of mild renarcotization 8 to 24 hr later (P = 0.0002) (Fig. 1). Renarcotization rates (25 to 33%) did not differ across trials (P > 0.99). We observed various combinations of open-mouth breathing, hypermetria, ataxia, and subtle changes in behavior and responsiveness in the 10 cases where renarcotization was diagnosed. Narcotic effects subsided ≤24 hr after onset, and none of the cases warranted administration of additional antagonist.

DISCUSSION

In evaluating and comparing naltrexone doses in elk, we regarded both rapid antagonism and complete protection from renarcotization as essential criteria in determining a minimum effective dose. Based on our data, we suggest that initial reversal of carfentanil immobilization in elk can be accomplished with as little as 13 mg IV naltrexone. Increasing the naltrexone dose failed to reduce initial recovery times (P = 0.31); a 20-fold increase in naltrexone dose reduced mean recovery times <1 min (Fig. 1). In a previous study, Haigh (1991) evaluated naltrexone (IM or IV), naloxone, and naloxone and diprenorphine in combination as antagonists of carfentanil and xylazine immobilization in

captive wapiti (*C. elaphus*). Mean recovery (to standing) times using IM or IV naltrexone were comparable to mean recovery times under other antagonist regimes tested. Recovery times in our study were more rapid (<9 min) and consistent (Fig. 1) than those reported by Haigh (1991), despite our using higher carfentanil dosages (10 μg/kg vs. about 3.7 μg/kg) and a wider range of naltrexone doses; use of xylazine in Haigh's (1991) study may have contributed to these differences.

The apparent increase in mean recovery times across our three trials could have been caused by cumulative carryover effects of repeated carfentanil or naltrexone administration. Alternatively, opiate antagonist-endocrine system interactions (Booth, 1988) could have somehow affected responses to naltrexone: these trials were conducted in the weeks preceding the peak of estrus in our captive elk herd, and the trend of increasing recovery times was most evident in the eight females, where mean (±SE) recovery times ranged from 2.8 (±0.5) min in trial 1 to 4.5 (±0.4) min in trial 3 as compared to a range of 3.3 (±0.3) min in trial 1 to 4.0 (±1.1) min in trial 2 for castrated males. A third possibility is that the observed trend could simply represent a random event. Potential mechanisms underlying this trend may deserve further investigation. Regardless of underlying cause, however, this increase in mean recovery time did not diminish the overall effectiveness of naltrexone in antagonizing carfentanil immobilization. Recovery times were not influenced by naltrexone dose, individual variation among animals, or interactions of dose and trial.

Although recovery times were consistent across the dose range tested, lowering naltrexone doses below 100 mg/mg carfentanil dramatically elevated renarcotization rates (Fig. 1). Observed effects of renarcotization were behavioral or occasionally locomotor, and closely resembled previous observations of renarcotization in elk after antagonizing carfentanil immobilization with naloxone HCl (Haigh, 1991; M. W. Miller, unpubl.). We judged these effects to be relatively mild within our experimental context, but such effects could potentially lead to harm for elk in the wild. Consequently, we recommend using 100 mg naltrexone/mg carfentanil as a minimum effective dose needed to provide both rapid antagonism of carfentanil immobilization and protection from renarcotization in elk. Because initial recovery from carfentanil immobilization can be accomplished with only small amounts of naltrexone IV, we further recommend dividing the antagonist dose between IV and SC routes to prolong systemic availability of naltrexone in order to aid in preventing renarcotization.

The only case of renarcotization in 130 immobilizations reported by Haigh (1991) occurred in a naloxone-treated cow. Naltrexone doses in that study varied widely (92 to 333 mg/mg carfentanil), but all exceeded doses (25 to 50 mg naltrexone/mg carfentanil) associated with renarcotization in our study. Moreover, the signs of renarcotization we observed were quite subtle and transient in most affected elk, and could easily have been overlooked without careful observation of affected individuals. Because investigators may vary in how they assess the severity of renarcotization, standardized methods for quantifying these observations probably should be developed. We suggest quantifying the severity of renarcotization (scored 1 to 4) by awarding cumulative points for abnormalities in the animal's behavior, gait, coordination, or level of consciousness attributable to narcotic agonism to allow more rigorous measurement of renarcotization within and among future studies.

Our experiment was conducted under optimal conditions, and our recommendations should be considered in that context. Elk were weighed just prior to immobilization, thereby allowing accurate calculation of both carfentanil and naltrexone doses, and deep intramuscular delivery of carfentanil was assured by hand-injection. Under field conditions using aerial

dart deliveries, carfentanil absorption and metabolism may be slowed by depositing drug in SC, fat, or connective tissues, or in damaged muscle tissue or hematomas associated with dart impact (Mueleman et al., 1984, Haigh, 1991). Delivering carfentanil remotely increases induction time, presumably by impairing drug absorption (Mueleman et al., 1984; Haigh, 1991); if metabolism and clearance of carfentanil were similarly impaired, renarcotization could occur.

This study was not designed to test protection against renarcotization in cases where carfentanil was absorbed slowly over a period of several hours from SC or fat deposits. However, based on responses of two elk only partially immobilized during our first trial, we believe we may have inadvertently deposited carfentanil SC or in fat in those two animals. Both cows were affected but still standing about 35 min after receiving carfentanil, so we gave each of them 100 mg naltrexone/mg carfentanil SC. Because one of these elk had mild signs of renarcotization about 24 hr later, higher naltrexone doses may be needed to prevent renarcotization in cases where poor carfentanil absorption is suspected. Similarly, more naltrexone may be needed to prevent renarcotization when carfentanil dosages >10 μg/kg body weight are used. In situations where higher antagonist doses might be deemed necessary, we observed no adverse effects of naltrexone doses ≤500 mg/mg carfentanil.

Our findings support earlier findings (Schmitt and Dalton, 1987; Allen, 1989; Haigh, 1991) that naltrexone HCl is safe and effectively antagonizes carfentanil immobilization in a variety of wild ungulate species. Naltrexone offers tangible advantages over opiate antagonists like diprenorphine, nallene, naloxone, and nalmefene, all of which have either significant agonist activity or a short metabolic half-life. Dosed at 100 mg/mg carfentanil, we believe that naltrexone HCl will provide safe and effective antagonism of carfentanil immobilization in elk under captive or free-ranging conditions.

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