Article

Intranasal naltrexone and atipamezole for reversal of white-tailed deer immobilized with carfentanil and medetomidine

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Abstract — Carfentanil and medetomidine were used to immobilize 8 captive female white-tailed deer *(Odocoileus virginianus)* using mean dosages [± standard deviation *(s)*] of 14.2 ± 1.11 μg/kg carfentanil and 17.8 ± 2.03 μg/kg of medetomidine. Deer were reversed by intranasally or intramuscularly administered naltrexone and atipamezole. Dosages of carfentanil and medetomidine proved reliable for immobilization of most, but not all deer, with a mean induction time of 13.3 ± 3.13 min. Effective and reliable immobilization will require higher dosages of carfentanil and possibly medetomidine than were used in this study. No significant differences in recovery times were observed for deer given reversal agents intranasally (9.45 ± 5.37 min) versus intramuscularly (7.60 ± 4.42 min). Naltrexone and atipamezole can be administered intranasally at 1.5 mg/kg and 0.1 mg/kg, respectively to safely and quickly reverse the effects of carfentanil and medetomidine in immobilized white-tailed deer. This route could potentially be useful for other reversal agents.

Résumé — Naltrexone et atipamézole par voie intranasale pour renverser l'immobilisation d'un cerf de Virginie par carfentanil et médétomidine. Le carfentanil et la médétomidine ont été utilisés pour immobiliser 8 cerfs de Virginie femelles en captivité *(Odocoileus virginianus)* en utilisant des doses moyennes [± écart-type] de 14,2 ± 1,11 μg/kg de carfentanil et de 17,8 ± 2,03 μg/kg de médétomidine. L'immobilisation des cerfs a été désactivée en administrant du naltrexone et de l'apimézole par voie intranasale ou intramusculaire. Les doses de carfentanil et médétomidine se sont avérées fiables pour l'immobilisation de la plupart des cerfs, mais pas tous, avec un temps d'induction moyen de 13,3 ± 3,13 min. Une immobilisation efficace et fiable exigera des doses supérieures de carfentanil et peut-être de médétomidine à celles utilisées dans cette étude. Aucune différence significative des temps de récupération n'a été observée pour les cerfs ayant reçu des agents déactivateurs par voie intranasale (9,45 ± 5,37 min) par rapport à l'administration par voie intramusculaire (7,60 ± 4,42 min). Le naltrexone et l'atipamezole peuvent être administrés par voie intranasale à 1,5 mg/kg et à 0,1 mg/kg, respectivement, afin de renverser les effets du carfentanil et de la médétomidine de manière sûre et rapide chez les cerfs de Virginie immobilisés. Cette méthode pourrait potentiellement être utile pour d'autres agents déactivateurs.

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Introduction

In North America, wildlife immobilization is often carried out by professional biologists or ecologists who work for government agencies and immobilize wild animals for a variety of purposes, including research and management of populations. Many of the antagonist drugs used for reversing chemically immobilized wildlife must be given partially, or completely intravenously (1,2) in order to have the desired effect, but field personnel involved with wildlife immobilization may have limited or no experience with intravenous (IV) or intramuscular (IM) drug administration methods (3). A previous study using intranasal xylazine to sedate physically restrained elk *(Cervus*

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elaphus) has shown that clinical effects were observed sooner than intramuscularly administered xylazine and nearly as quickly as with intravenous administration of this drug (3).

Intranasal (IN) administration of sedative drugs is safe and effective for short-term sedation and restraint in humans (4–6), domestic dogs *(Canis familiaris)* (7), elk (3), domestic rabbits *(Oryctolagus cuniculus)* (8), and ring-necked parakeets *(Psittacula krameri)* (9). Intranasal drug administration is generally easier for lay personnel in the field, has fewer and less severe complications, and requires less training and experience than IV drug administration. Intramuscular injections are also technically easy to administer, but drugs administered IN may be more rapidly absorbed due to the high volume of potential surface area for absorption, and the drug may be delivered directly to the brain in some species (10). Intranasal administration also avoids problems with first-pass metabolism of drugs metabolized by the liver, and may be associated with fewer side effects. In addition, drug combinations for white-tailed deer *(Odocoileus virginianus)* that consist of opioids in combination with alpha-2 agonists lack ideal immobilization characteristics and have resulted in significant side effects for subject animals (11,12). Carfentanil, one of the most potent and rapid acting opioids, to our knowledge, has not been previously combined with medetomidine, a potent alpha-2 agonist and evaluated as a field anesthetic for white-tailed deer. The synergistic effect of these 2 drugs in combination has potential for an extremely low volume, rapid onset, drug combination with few complications for deer and potentially larger cervids such as moose *(Alces alces)* and elk. The objectives of this study were to determine if carfentanil and medetomidine could be used to effectively immobilize white-tailed deer for short field procedures, and to compare the efficacy of IN and IM administration of atipamezole and naltrexone as reversal agents for carfentanil and medetomidine in white-tailed deer.

Materials and methods

Eight captive adult female white-tailed deer housed at the Alternative Livestock Research Facility of the University of Saskatchewan located near Saskatoon, Saskatchewan (52° 02′ N and 106° 28′ W) were used for this study. They were kept on native grass and alfalfa pasture and ranged in age from 3 to 7 y. Each deer was immobilized on 2 separate occasions in a crossover trial between September 5th and 14th, 2006 with a 7-day washout period to allow metabolism of the drugs between immobilization events. Deer were manually herded into a large corral and selected deer were dart injected with a combination of carfentanil citrate (Wildnil, ZooPharm, Fort Collins, Colorado, USA) and medetomidine hydrochloride (Domitor, Pfizer Animal Health, Kirkland, Quebec) using a 2-mL Dan-Inject dart syringe delivered remotely using a Dan Inject JM CO2 powered rifle (DanInject, Fort Collins, Colorado, USA). A standardized dose of 1.2 mg medetomidine hydrochloride (1 mg/mL) and 0.9 mg carfentanil citrate (3 mg/mL) was used for immobilization based on previously published dosages of carfentanil and xylazine and prior clinical experience using carfentanil and other alpha-2 agonists in deer and other ungulates. A medetomidine dosage of approximately 20 μg/kg was chosen as the target dosage based on etorphine-xylazine combinations recommended for use in white-tailed deer (1), assuming a clinical equipotency of approximately 15 times for medetomidine compared to xylazine (13). A carfentanil dosage of approximately 15 μg/kg was used initially to determine if side effects seen with other opioid-alpha-2 combinations could be avoided or significantly reduced. Injections were targeted in the large muscles of the hind leg and time until first signs of ataxia, sternal recumbency, and loss of consciousness were recorded for each immobilization event.

All deer were blindfolded when deemed safe to approach and some were physically restrained in lateral recumbency when necessary. Vital rates (pulse, respiration, rectal temperature) were recorded every 10 min and between 15 and 20 min post-injection an arterial blood sample was obtained for blood gas analysis from the auricular artery, which was catheterized using a 22-gauge over-the-needle catheter. Blood pressure measurements were recorded directly through this catheter using a Surgivet V6400 (Smiths Medical North America, Waukesha, Wisconsin, USA) physiological monitor. Blood gas parameters were immediately evaluated using a field i-STAT Portable Clinical Analyzer (i-STAT Corporation, East Windsor, New Jersey, USA). Reversal of immobilization was accomplished by simultaneously administering 1.5 mg/kg (50 mg/mL) naltrexone HCl (Voigt Global Distribution LLC, Kansas City, Missouri, USA) and 0.1 mg/kg (5 mg/mL) of atipamezole hydrochloride (Antisedan; Novartis Animal Health, Mississauga, Ontario) either IM or IN. Intranasal drug administration was accomplished by inserting a 3 French catheter into the ventral nasal meatus and advancing the tip to the level of the medial canthus of the eye (approximately 8 cm) and injecting the naltrexone in one nasal cavity and the atipamezole in the opposing nasal cavity with separate syringes. The head and neck were briefly held elevated in a horizontal position and maintained there until no liquid was visible running out of the nasal cavity. Differences in arousal times (time to sternal recumbency, standing, and head up) were assessed using a paired 2-sample *t*-test that assumed unequal variance (Microsoft Excel) with differences considered to be significant if P was < 0.05. All procedures used during this study were approved by the University of Saskatchewan Committee on Animal Care and Supply, Protocol number 2006-0048.

Results

The carfentanil/medetomidine combination proved to be unreliable at the dosages used for consistently immobilizing captive white-tailed deer. There was no significant difference between immobilization parameters between 1st and 2nd immobilization attempts for each animal. For immobilization attempts during which deer actually became recumbent with the initial dose (n = 14), the mean carfentanil dosage ($\pm$ s) was 14.2 $\pm$ 1.11 μg/kg and medetomidine dosage was 17.8 $\pm$ 2.03 μg/kg. These deer became initially ataxic at 7.33 $\pm$ 2.48 min, became sternally recumbent at 11.4 $\pm$ 3.53 min, and were unconscious at 13.3 $\pm$ 3.13 min after dart injection. Inductions were characterized by long periods of hypermetria in some cases. Two of the 16 immobilizations did not result in complete immobilization and the deer had to be manually restrained prior to becoming recumbent on their own.

Table 1. Blood gas data and physiological parameters for white-tailed deer ($n = 9$) immobilized with carfentanil-medetomidine

Parameter	Mean ± *s*	Range
Systolic arterial pressure (mmHg)	173.4 ± 22.7	146–224
Diastolic arterial pressure (mmHg)	116.6 ± 20.0	86–145
Mean arterial pressure (mmHg)	136.4 ± 15.0	112–160
PaO_2 (mmHg)	61.0 ± 7.05	50–71
$PaCO_2$ (mmHg)	51.4 ± 5.23	43.2–61.0
Bicarbonate (mmol/L)	25.6 ± 3.99	20.8–31.3
Base excess (mmol/L)	−1.44 ± 4.61	−7–6
Lactate (mmol/L)	1.84 ± 0.37	1.39–2.58
pH	7.32 ± 0.07	7.22–7.41
Rectal temperature (°C)	40.5 ± 0.8	39.4–42.6
Respiration (breaths per min)	22.5 ± 10.0	10–40
Heart rate (beats per min)	54.2 ± 8.9	45–71

s — standard deviation.

Table 2. Mean recovery times for white-tailed deer immobilized with carfentanil-medetomidine and reversed via intramuscular injection or intranasal delivery of naltrexone and atipamezole

	Recovery time (min)			
	Intramuscular ($n = 7$)		Intranasal ($n = 7$)	
Parameter	Mean ± *s*	Range	Mean ± *s*	Range
Time to head up	2.92 ± 2.28	0.6–7.5	6.83 ± 2.18	0.3–17
Time to sternal recumbency	5.97 ± 3.98	2.5–12.3	9.10 ± 5.82	1.3–17.5
Time to standing	7.60 ± 4.42	2.9–15.1	9.45 ± 5.37	3.5–17.5

s — standard deviation.

These 2 deer showed signs of moderate ataxia, typical hackneyed gait, and mild excitement, which are typical of low-dose narcotic administration in wild ungulates (12). Data from these deer were excluded from all calculations, as they did not become fully immobilized from the carfentanil/medetomidine combination. Four of the remaining 14 immobilizations were considered successful, but less than ideal as deer became recumbent, but were in a light plane of anesthesia, requiring minimal manual restraint during handling, and data from these deer were included. Two of these deer were from the IM group and 2 were from the IN group, so there was no effect on subsequent reversal. All other immobilizations ($n = 10$) were successfully performed and allowed deer to be approached for blindfold application without arousal. Most immobilized deer were initially in sternal recumbency, but were in lateral recumbency when deemed safe to approach.

No significant differences were observed between the 1st and 2nd immobilizations for any of the measured physiological parameters in deer that were successfully immobilized both times, so data are pooled from all animals that were successfully immobilized and had physiological data taken ($n = 9$) and summarized in Table 1. All deer were moderately hypertensive, moderately to severely hypoxemic and developed moderate metabolic acidosis during anesthesia. Most deer developed slight hyperpnea and bradycardia as a result of immobilization with carfentanil-medetomidine (Table 1). All deer were successfully reversed with naltrexone and atipamezole using the dosages administered, regardless of delivery method (Table 2). Individually, there were no significant differences in time to standing, head up, or sternal recumbency between reversal agents administered IN or IM, although the mean times for each group were longer for deer given reversal agents IN. No episodes of renarcotization or resedation were observed for any deer up to 24 h post-immobilization.

Discussion

The combination of carfentanil and medetomidine has not been evaluated for use as an immobilizing combination for domestic or wild animals. Carfentanil and xylazine have been widely used for immobilization of captive and free-ranging white-tailed deer and other cervids, but hyperthermia, excitation, muscle rigidity and hypoxemia have occurred to varying degrees with this combination (11,14,15). Medetomidine is a widely used potent alpha-2 agonist for chemical immobilization of a variety of species in combination with dissociative anesthetics such as ketamine and tiletamine/zolazepam combinations (1,16). It has also been combined with opioid drugs such as butorphanol for anesthesia of captive red wolves *(Canis rufus)* (17) and sedation and anesthesia of domestic dogs (18) and pigs *(Sus scrofa)* (19). Medetomidine (1 mg/mL) is sold commercially in Canada and is licensed for use as a sedative in dogs, but it has been increasingly used for the past decade in wildlife species in an extra-label manner, employing more potent formulations ranging from 10 to 30 mg/mL. There are no established withdrawal times for medetomidine and most other immobilization drugs when used in deer or other cervid species in Canada.

Carfentanil citrate is available in the United States and Canada as a compounded product through specialty pharmacies. Recommended withdrawal times for meat in carfentanil are typically 30 d for wild cervids (20,21). The dosages chosen for medetomidine and carfentanil were approximations based on previously published dosages of carfentanil and xylazine (a less potent similar alpha-2 agonist) for white-tailed deer (22,11,14). Relatively low dosages of each drug were initially chosen due to the potential for cardiorespiratory depression from the combination of carfentanil and medetomidine, both of which can impair oxygenation and cause hypoxemia.

Based on the results obtained, this combination is not reliable for consistent and effective immobilization of white-tailed deer at the dosages used. Approximately 62.5% (10 of 16) of the immobilization attempts were considered completely successful at this dosage. Twenty-five percent (4 of 16) were not ideal, but the deer could still be handled, and 12.5% (2 of 16) were considered unsuccessful because in a free-ranging situation the deer would likely not have been successfully immobilized and restrained. The drug dosages were also determined from prior studies with captive animals that had been previously handled (22). The deer in the current study were not accustomed to handling, and a higher dose should have been considered. Free-ranging deer would probably require a significantly higher dose than the captive animals. A carfentanil dosage of approximately 0.03 mg/kg would likely be required to reduce the long induction period and improve the quality of the immobilization. This combination has potential if concentrated medetomidine is used, as a useful, very low volume (< 1 mL total) alternative to other combinations such as carfentanil and xylazine for field anesthesia of white-tailed deer, but further study will be required

to optimize the dosages. It also has potential for larger cervid species such as moose and elk, which often require high volume doses of immobilization drugs (1).

Significant hypoxemia without hypercapnea was observed at the dosages used and potent opioids administered with alpha-2 agonists have been demonstrated to produce significant respiratory depression in deer and other species when combined, due to their potent synergistic effect (23–27). This combination produced significant hypoxemia in these white-tailed deer that was greater than that observed with carfentanil-xylazine (14) and almost as severe as carfentanil-xylazine-ketamine combinations (15) used in white-tailed deer. Hypoxemia was not as severe as in white-tailed deer immobilized with BAM (butorphanol, azaperone, medetomidine) that did not receive supplemental oxygen (25), even though very similar medetomidine dosages were used. Due to the significant levels of hypoxemia observed, it is recommended that supplemental oxygen always be administered to deer immobilized with this combination. The observed mild hypertension was most likely due to medetomidine, which causes hypertension in combination with ketamine (16,17,26), due to peripheral vasoconstriction that tends to resolve over time in most species (22,23,26). Similar effects are observed with carfentanil in many species (28,29). Hypertension can result in a reflex bradycardia (23,27) that can significantly decrease cardiac output (23). If serial samples had been taken later in the immobilization, rather than just the single blood pressure measurement, this may have been apparent. Hypertension was not profound in these animals but tended to be higher than that induced by medetomidine-ketamine or carfentanil-xylazine in mule deer and white tailed deer/mule deer hybrids (22). Carefully controlled clinical trials will be required to determine optimal dosages resulting in safe anesthesia without severe complications and side effects such as hypoxemia or decreased tissue oxygen delivery resulting from decreased cardiac output.

Both IN and IM administration of atipamezole and naltrexone rapidly and effectively reversed the effects of both medetomidine and carfentanil respectively without evidence of resedation or renarcotization. Although there were no significant differences between reversal times for antagonists administered IM or IN, mean reversal times were slightly longer for antagonists administered IN. This was likely due to the wide range of values that occurred for deer reversed IN (Table 2). This variability may have been due to a number of factors creating individual differences in nasal absorption such as patient positioning, potential for drug administration into the nasal choana or nasopharynx (30), or because some deer were hyperthermic, absorption may have been enhanced due to peripheral vasodilation. Low molecular weight compounds, such as immobilizing drugs which are $<$ 1000 daltons, are absorbed across the nasal mucosa much faster than larger compounds like proteins and may even be absorbed directly into the brain without going through the systemic circulation (31), but this did not seem to be the case for this study as IN administration was no more rapid than IM administration. In addition, times to head up and sternal recumbency, although not significant, were generally longer for the IN group, even though time to standing was quite similar. This may be a result of differing pharmacokinetics or may indicate more rapid and complete absorption from the IM injection site. Intranasal naloxone has been shown to be as safe and effective as IV administration for treatment of opioid overdose in humans (32,33). Naltrexone has been shown to be effective for reversal of a number of potent opioid drugs in wild and captive animals including carfentanil and etorphine by a variety of routes including SQ, IM, and IV (1). To our knowledge, this is the first report of the effective use of naltrexone or atipamezole administered IN for reversal of immobilization drugs. The large variability in individual drug response in this study could potentially be reduced through the use of an atomizer to distribute the drug more evenly across the nasal mucosa. Chitosan solutions (34) that increase the bioavailability of intranasally administered drug could also be used to enhance absorption. Other commonly used alpha-2 reversal agents for wildlife immobilization that are routinely administered IV, such as yohimbine and tolazoline could potentially be administered intranasally safely and effectively, but additional studies would be required. Withdrawal times for cervid species have not been established for drugs that are administered by the intranasal route, as is the case for most drugs used in wildlife species.

In conclusion, atipamezole and naltrexone were effective at reversing carfentanil and medetomidine anesthesia in white-tailed deer via either the intramuscular or intranasal route. Reversal times were similarly rapid regardless of administration route, but IN administration is potentially much easier for untrained field personnel than is IV administration, which is commonly used for reversal of immobilization drugs in wildlife species. However, IN administration did not seem to confer any advantage over IM administration. Carfentanil and medetomidine have potential to be used as a low volume immobilization combination for wild cervids, but higher dosages of carfentanil and possibly medetomidine are necessary for consistent and reliable immobilization of white-tailed deer. Based on physiological parameters and compared to earlier studies, there may be little benefit to this combination over carfentanil-xylazine. Both combinations induce physiologically significant hypoxemia. There was a trend towards increased blood pressure in the current study that may negate any benefits of volume reduction. Given the degree of hypoxemia with this combination supplemental inspired oxygen should be administered.

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