XYLAZINE IMMOBILIZATION OF MOOSE WITH YOHIMBINE OR TOLAZOLINE AS AN ANTAGONIST; A COMPARISON TO CARFENTANIL AND NALTREXONE

Charles C. Schwartz, Thomas R. Stephenson and Kris J. Hundertmark

Alaska Department of Fish and Game, Moose Research Center, 34828 Kalifornsky Beach Road, Suite B, Soldotna, AK 99669

ABSTRACT: When moose (*Alces alces*) are kept in captivity, it is often necessary to immobilize them for research purposes or animal care. Carfentanil, a very potent narcotic, used in combination with xylazine hydrochloride is the preferred drug mixture when immobilizing moose in the wild. However, carfentanil is both expensive and potentially dangerous to the handler. We evaluated the use of xylazine hydrochloride, an alpha$_2$ adrenergic sedative and analgesic, used alone, or in combination with either carfentanil citrate or ketamine hydrochloride to immobilize moose at the Moose Research Center. Mean down time for xylazine alone was not different from xylazine:ketamine and carfentanil:xylazine mixtures. Drugged animals could be approached and handled immediately when given carfentanil:xylazine. Xylazine or xylazine:ketamine drugged animals often lay down 8-12 minutes before completely immobilized. The antagonist yohimbine had no apparent effect on reversal of xylazine - immobilized moose, and recovery times averaged 3:38 $\pm$ 2:01 hours. The antagonist tolazoline hydrochloride reduced recovery times significantly ($P<0.0001$), and animals reversed with this drug were standing within 4 to 31 minutes ($\bar{x} = 21$ minutes). Animals immobilized with a mixture of carfentanil:xylazine and reversed with naltrexone were usually standing within 7 minutes with a range from 3 to 21 minutes after administration of the antagonist. Comparisons of individual drugs, mixtures and antagonists are discussed relative to cost, efficiency, effectiveness, safety, and reliability of immobilizing moose.

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In the past 2 decades, a wide variety of drugs have been used to immobilize moose (Franzmann and Arneson 1974, Gasaway *et al.* 1978, Franzmann 1982, Schmitt and Dalton 1987). Today, carfentanil citrate, a synthetic opiate used in combination with xylazine hydrochloride, a sedative analgesic, works well to immobilize moose (Haigh 1982; Franzmann *et al.* 1984, 1987; Seal *et al.* 1985; Schmitt and Dalton 1987). The extreme potency of carfentanil, however, can be dangerous to humans (Haigh 1990). This characteristic, together with licensing regulations, makes the use of potent narcotics unattractive to many individuals. Accidental administration of carfentanil to humans during capture operations is a primary safety concern. This is especially important when darting animals in urban areas where human bystanders are likely present, or when errant darts are not retrieved. As a consequence, it would be desirable from a human safety perspective if moose could be immobilized effectively and reversed with an antagonist without requiring carfentanil.

Xylazine hydrochloride used alone or in combination with ketamine hydrochloride has been an effective immobilization agent on a wide range of domestic and wild ruminants (Franzmann 1982, Jessup *et al.* 1983, Hsu and Shulaw 1984, Seal *et al.* 1985, Kreeger *et al.* 1986, Takase *et al.* 1986, DelGiudice *et al.* 1989, Doherty and Tweedie 1989, Golightly and Hofstra 1989, Garner and Addison 1994). Xylazine is a potent sedative-analgesic agent which may cause significant depression of the central nervous system (Zingoni *et al.* 1982, Hsu *et al.* 1987)

and respiratory distress characterized by tachypnea (Zingoni *et al.* 1982, Hsu *et al.* 1987) and hypoxema (Doherty *et al.* 1986, Waterman and Livingston 1987).

Xylazine sedation may result in cervids being immobilized for 3-6 hours and occasionally up to 12 hours (Mech *et al.* 1985). Therefore, an antagonist would be beneficial to safeguard the use of xylazine and reduce prolonged immobilization. Xylazine has been reversed with yohimbine, tolazoline, and idazoxan in several ruminant species, but effectiveness varies among species. In moose and caribou (*Rangifer tarandus*) as well as domestic cattle and sheep, yohimbine produces only partial reversal. According to Nolan *et al.* (1986), yohimbine usually is more effective in nonruminants than tolazoline in antagonizing the pharmacological effects of xylazine. In ruminants however, tolazoline is more effective than yohimbine in this respect (Hsu *et al.* 1987, Takase *et al.* 1986, Guard and Schwark 1984). Yohimbine (0.8 mg/kg) has also been reported to be lethal in xylazine-treated sheep (Hsu et al 1987). Idazoxan appears effective in sheep (Hsu *et al.* 1989), moose and caribou (Doherty and Tweede 1989), but is an experimental drug not available commercially in the United States. We tested two commercially available antagonists, yohimbine hydrochloride and tolazoline hydrochloride as an antidote to xylazine in moose. We compare these results to moose immobilized with mixtures of xylazine and carfentanil antagonized with naltrexone.

METHODS

The study was conducted with captive moose at the Moose Research Center, a research facility of the Alaska Department of Fish and Game on the Kenai Peninsula. Most moose were maternal-reared although a few were bottle-reared. Animals were maintained on natural vegetation within the enclosure and supplemented with a pelleted ration (Schwartz *et al.* 1985). All test dosages of immobilization agents were administered by intramuscular injection by hand with a syringe as the animal stood on a scale for weighing. Xylazine hydrochloride (Rompun®, Chemagro Division of Bay Chemical Corp., Kansas City , Mo.) when used alone was administered at dosages ranging from 1.1 to 2.8 mg/kg body weight. Dosages of xylazine when mixed with ketamine or carfentanil, were 0.9 to 1.1 mg/kg, and 0.1 to 1.9 mg/kg, respectively. Carfentanil (Wildnil, Wildlife Pharmaceuticals, Inc. Fort Collins, Co) was dosed at 2.5 to 9.3 μ/kg, and ketamine hydrochloride (Ketaset, Aveco Co., Fort Dodge, Iowa) at 0.4 to 0.5 mg/kg. Each drug and dosage were given at approximately standard concentrations for each age class of animal (cow, bull, calf) rather than calculated on a predetermined mg/kg basis determined by measured body mass. We did this because this more closely matches the way drugs are administered under field conditions where it is impossible to weigh the animal. Here we present data as both standard dosage (mg/animal) and on a mg/kg basis for comparison purposes.

Antagonists tested were yohimbine hydrochloride (Antagonil™, Wildlife Pharmaceuticals, Inc. Fort Collins, Co.) and tolazoline hydrochloride (Priscoline®, Ciba Pharmaceutical Co. Summit, N. J.). Yohimbine was dosed at a low ($\bar{x}$ = 0.1 mg/kg , range 0.05 to 0.13) and a high dosage ($\bar{x}$ = 0.35 mg/kg, range 0.25-0.50). Tolazoline was dosed at 25 mg/100 mg xylazine ($\bar{x}$ = 0.4mg/kg). Naltrexone (50 mg/ml) was dosed at 100 mg/mg carfentanil (0.3-0.8 mg/kg).

We defined down time as the time in minutes from injection of the immobilizing agent until the animal assumed sternal recumbency. We did not measure true induction time (time from injection to onset of anesthesia) because this required repeated checks of the animal to monitor level of sedation and in our experience animals dis-

turbed after reaching sternal recumbency but not yet completely sedated became hypersensitive and often required additional drug and/or more time before sedation was attained. For that reason, we only noted when the animal lay down but routinely waited an additional 5-10 minutes for full effect. Recovery time is the time in hours and minutes from injection of the antagonist until the animal was standing. Immobilized time is defined as the time from sternal recumbency following injection of the immobilizing agent until the animal was standing.

We compared down times for xylazine (X) alone, and as a mixture with carfentanil (X:C), and ketamine (X:K) using a Kruskal-Wallis Test (Conover 1980). Recovery time was compared for X using yohimbine (X:Y) and tolazoline (X:T) as the antagonists, for X:K mixture with yohimbine (X:K:Y) and tolazoline (X:K:T) as antagonist, and for a X:C mixture with tolazoline and naltrexone (X:C:T:N) or only naltrexone (X:C:N) as the antagonist. Data were tested using a one-way ANOVA (Winer *et al.* 1991). To meet normality and homogeneity of variance assumptions, data were converted to natural logs. Based on a Wilk's W statistic (D'Agostino and Stephens 1986) the normality assumption did not appear to be violated, and a Sperman rank correlation between the absolute value of the model residuals and the predicted values was non-significant providing evidence that the homogeneity of variance assumption was met (Carrol and Ruppert 1988). We used Tukey's honestly significant difference (HSD) test (Weiner *et al.* 1991) to determine differences among treatment means.

RESULTS

Moose immobilized with xylazine alone assumed sternal recumbency within approximately 4 minutes of injection ($\bar{x} \pm$ s.d. = 4:10 $\pm$ 2:40 , range 1 to 12 min.). Immobilization time averaged about 3:02 h (s.d. = 1:07) (Table 1), generally with animals receiving higher dosages of drug remaining down for longer periods. Although immobilized animals lay down within 1-12 minutes of injection of xylazine, complete immobilization required an additional 10 to 15 minutes. Animals approached too soon after assuming sternal recumbency often stood or attempted to stand; some overcame the effect of the drug. Once excited, the initial dose was usually ineffective in sedating the moose and supplemental dose(s) were required.

Down times for X:K injection ($\bar{x} \pm$ s.d.= 4:24 $\pm$ 2:31 min., range 2 to 8 min.) and X:C injection ($\bar{x} \pm$ s.d.= 4:47 $\pm$ 4:18 min., range 2 to 20 min.) were not different from X alone (Table 1), (P =0.271). Animals immobilized with 8.1 µg/kg carfentanil and 0.4 mg/kg xylazine, when compared to animals given higher doses of xylazine (1.4 mg/kg) and a reduced dose of carfentanil (3.1 µg/kg) had shorter induction times with much reduced standard deviations, suggesting more consistent results. A dosage of 2.5-3.0 mg of carfentanil and 100-200 mg xylazine per adult cow moose provided the most reliable immobilization with the most consistent results.

Recovery times varied significantly (ANOVA, $df_{5,48}$, $P < 0.0001$) among antagonists (Table 1). High and low doses of yohimbime produced similar (P>0.05) results and were combined for purposes of discussion. Yohimbine did not provide reliable antagonism to xylazine ($\bar{x} \pm$ s.d.= 3:38 $\pm$ 2:01 h) or X:K ($\bar{x} \pm$ s.d.= 1:59 $\pm$0:45 h) mixtures. We did not detect (P = 0.497, t = 0.008) reduced recovery times when compared to animals given xylazine and no antagonist ($\bar{x} \pm$ s.d.= 3:02 $\pm$ 1:47 h). Animals reversed with tolazoline stood significantly ($P < 0.0001$) sooner when compared with yohimbine (Table 1). It took longer for tolazoline to reach full effect in animals given straight xylazine ($\bar{x} \pm$ s.d.= 21:24 $\pm$ 9:17 min., range 10 to 31 min.) compared with the

Table 1. Immobilization agent, dosage, induction time, antagonist and recovery time for drugs and their antagonist used to immobilize moose at the Moose Research Center, Kenai Peninsula, Alaska. Standard deviations are provided in parentheses.

Immobilization Agent	*n*	Dose (mg/kg)[a]	Induction Time Hr:Min	Recovery Antagonist	Recovery Time Hr:Min
Xylazine (X)	18	1.7 (0.4)	0:04.2 (0:02.7)	None	3:02 (1:07)
X	5	1.6 (0.3)	0:18.2 (0:15.2)	Tolazoline (T)	0:21 (0:09)B[b]
X	7	2.2 (0.5)	0:07.4 (0:08:3)	Yohimbine (Y)	3:38 (2:01)A
X:Ketamine (K)	5	1.4 (0.3):0.4 (0.03)	0:08.0 (0:03:3)	T	0:14 (0:07)BC
X:K	5	1.1 (0.1):0.6 (0.02)	0:04.4 (0:02.5)	Y	1:59 (0:45)A
X:Carfentanil (C)	6	1.4 (0.3):3.1 (0.5)	0:11.3 (0:07.5)	Naltrexone:T	0:09 (0:03)BC
X:C	21	0.4 (0.4):8.1 (1.4)	0:03.5 (0:00.5)	N	0:07 (0:05)C

[a] Dosage for carfentanil in μg/kg.

[b]Any two means followed by a different letter are significantly different ($P<0.05$) according to Tukey's Studentized Range (HSD) test.

X:K cocktail ($\bar{x} \pm$ s.d.= 14:24 ± 6:48 min , range 4 to 20 min.), but the means were not different statistically. Recovery times for moose drugged with X:C and reversed with either naltrexone ($\bar{x} \pm$ s.d.= 7:16 ± 4:59 min., range 3 to 21 min.) alone or combined with tolazoline ($\bar{x} \pm$ s.d.= 9:20 ± 3:23 min., range 5 to 15 min.) were not different. Recovery times for X:T were significantly longer than those for X:C:N (Table 1).

DISCUSSION

Xylazine and X:K mixtures can be used without carfentanil to successfully immobilize moose. For captive moose with a nervous disposition, to ensure successful induction of recumbency and sedation, xylazine dosages from 1.8 to 2.2 mg/kg are recommended. If ketamine is used in combination with xylazine, the xylazine dose can be reduced to 0.8 to 1.1 mg/kg with 0.4 mg/kg ketamine. For wild moose, or where there is a high level of external stimulation (i.e., noise), we recommend 2.6-3.0 mg/kg of xylazine based on our field experience.

We found yohimbine hydrochloride ineffective as an antagonist to xylazine and xylazine:ketamine mixtures in moose. Yohimbine is an alkaloid compound which is believed to block the adrenergic mechanisms stimulated by xylazine in the central alpha^2 adrenoreceptors (Hsu 1981, Goldberg 1983). Yohimbine has been used successfully to antagonize xylazine in a number of species including mule deer (*Odocoileus hemionus*) (Jessup *et al.* 1983), white-tailed deer (*O. viriginianus*) (Hsu and Shulaw 1984, Mech *et al.* 1985), fallow deer (*Dama dama*) (Stewart and English 1990), elk (*Cervus elaphus*) (Golightly and Hofstra 1989) and moose (Renecker and Olsen 1984, Garner and Addison 1994, but see below). Yohimbine decreased duration of ruminal stasis and bradycardia in domestic calves given xylazine but had no effect on sedation (Guard and Schwark 1984). Most scientists

using yohimbine report a short arousal period with animals able to stand in 2-7 minutes, with a dosage of around 0.125 to 2.0 mg/kg.

In our tests reported here, when yohimbine was administered to sedated animals we detected little or no response in respiration rate or state of arousal. We tested a low ($\bar{x}$ = 0.1 mg/kg, range 0.05 to 0.13) and a high dosage ($\bar{x}$ = 0.35, range 0.25-0.50). Garner and Addison (1994) tested yohimbine in moose immobilized with a ketamine:xylazine mixture (4:1 ratio) following calving in spring. Recovery time averaged 23 minutes, but the range was from 1 to 71 minutes. They concluded that recovery time following injection of yohimbine was variable regardless of time administered. Garner and Addison (1994) used large doses of ketamine relative to xylazine. Ketamine, a dissociative anesthetic agent is metabolized more rapidly than xylazine and it has no known antidote. Moose given yohimbine injections that are sedated primarily with ketamine are likely to respond more rapidly than xylazine-sedated animals independent of the antagonist. This is especially true if the animal has been under sedation for an extended duration prior to receiving the antagonist. The only other test that we are aware of with moose was reported by Renecker and Olsen (1985), but they tested yohimbine in combination with 4-aminopyridine which also acts as an alpha^2 antagonist, so results are not directly comparable.

Tolazoline, marketed as Priscoline hydrochloride for humans, is a direct vasodilator with moderate competitive alpha-adrenergic blocking activity. It is used primarily for the treatment of persistent pulmonary hypertension in newborn humans when systemic arterial oxygenation cannot be satisfactorily maintained by usual supportive care. It is a combined alpha^1 and alpha^2 adrenergic receptor antagonist (Hsu et al 1987, Gross and Tranquilli 1989), and has been used successfully to reverse the sedation effects of xylazine in domestic sheep (Hsu *et al.* 1987), mule deer (DelGiudice et al 1989), and white-tailed deer (Kreeger *et al.* 1986) but has met with mixed results in cattle (Kitzmann *et al.* 1982, Hikasa *et al.* 1988). Results for our studies indicate that moose can be reversed effectively with tolazoline. Antagonism effects were slower than those witnessed when reversing the effects of carfentanil with naltrexone. Most animals were standing within 15-20 minutes, with a few requiring 30 minutes. Some of the moose immobilized in our trials were sedated in order to transport them from one enclosure to another. This moving required that the animal be deeply sedated (2.6 - 3.0 mg/kg xylazine) for approximately 60 to 90 minutes during which time they were winched onto a snowmachine trailer and hauled 2.6 - 3.0 km distance. Tolazoline worked well in all cases. We agree with Gross and Tranquilli (1989) and Hsu *et al.* (1989) that tolazoline is more efficacious than yohimbine at antagonizing some effects of xylazine in ruminants, and specifically in moose.

We can only speculate as to why others have reported success with yohimbine in moose. Two of our moose responded to the yohimbine injection almost immediately. Yohimbine has various effects on cardiovascular reflexes. It is known to increase blood pressure and heart rate and can cause arousal as a result of stimulation of the central nervous system (Goldberg and Robertson 1983). Xylazine is a sedative but animals can override the effects when subjected to external stimulation, especially with lower doses. We speculate that what might happen when yohimbine successfully reverses xylazine is that much of the initial xylazine dose has been metabolized from the animal's, system and it is nearly ready to stand on its own accord. The yohimbine antidote acts more as a stimulant that helps the animal overcome the effects of the remaining xylazine. Animals with larger concentrations of xylazine

remaining in their system do not respond as rapidly to the antidote. This may explain the seemingly wide range of recovery times (1 to 71 min.) reported by Garner and Addison (1994). Additionally, moose in general tend to be less excitable than the smaller cervids and our tame moose were generally much less excitable than their wild counterparts. Consequently, if yohimbine only acts as a partial antagonist or more as a stimulant, one would expect the most excitable species and individuals to respond most positively to its effects. This may explain why yohimbine works on some ruminant species or individuals and not others.

Franzmann (1982), in his assessment of immobilization agents for moose listed 10 criteria that can be used when evaluating immobilizing drugs. These criteria are: (1) rapid absorption and action, (2) concentrated form - small quantity for injection, (3) wide range of tolerance for animal, (4) safe for handler, (5) reversible, (6) no side effects, (7) effective anesthesia level, (8) not subject to dangerous drug licensing, (9) cleared for use on animals for food, and (10) low cost. An ideal immobilization agent meets all 10 criteria. Carfentanil qualifies positively for some of the criteria, but is dangerous for the handler (Parker and Haigh 1982), subject to dangerous drug licensing, and it is expensive.

Xylazine hydrochloride used alone or in combination with ketamine hydrochloride is commonly used in captive moose (Franzmann 1982) and occasionally in the wild (Doherty and Tweedie 1989). Xylazine meets some of the 10 criteria except that is not an anesthetic and is not approved for food animals. Doherty and Tweedie (1989) tested two alpha$_2$ antagonists, idazoxan and its methoxy analogue RX 821002. Both provided rapid recovery of consciousness and most animals were up within 1.6 minutes. However idazoxan and its 2-methoxy analogue are not available commercially. Xylazine has been known to cause bradycardia and cardiovascular depression in ruminants (Hsu et al 1987). When used alone very large doses are required to achieve consistent and relatively fast immobilization. Prolonged recumbence can result in bloat and regurgitation (Doherty and Tweedie 1989), and hyperthermia and thermoregulation problems can occur up to 12 hr. post injection (Young 1979).

MANAGEMENT IMPLICATIONS

Xylazine costs approximately $32.00 per vial (5,000 mg). The cost to immobilize an adult cow moose (450 kg) using xylazine at a dosage of 2.2 mg/kg is only $6.34. Antagonism with tolazoline for this dose costs $1.41 bringing the total to $7.74 (Table 2). Cost of immobilization using a higher dosage increases proportionally (Table 2). Using a xylazine:ketamine (1.8:0.4 mg/kg) cocktail costs $6.98 for the immobilization and $1.15 for the antagonism, totaling $8.13. These values are about 1/7 to 1/8 the cost to immobilize a moose with a mixture of xylazine:carfentanil ($60.95)(Table 2). Of course, our calculations do not consider personnel time required to prepare drugs, time spent waiting for animals to go down and recover, and costs associated with fixed-wing and/or rotor aircraft.

Strictly from a drug expense, it is much more economical to immobilize moose without using a narcotic. However, the tradeoff must be considered. Xylazine is not concentrated and requires large dosages to ensure immobilization (up to 13 cc drug) and even then some animals can override the effect and stand. Xylazine can be concentrated which more than doubles the cost. Xylazine induction may require up to 30 minutes post injection before an animal can be safely handled. However xylazine is relatively safe for the handler. Tolazoline appears to be an effective antagonist to xylazine, but it may take animals up to 30 minutes to stand and move away. Tolazoline is relatively inex-

Table 2. Immobilization costs (1996 U.S $) for an average 450 kg adult cow moose using xylazine, xylazine:ketamine, and xylazine:cartentanil, and reversal with tolazoline and naltrexone.

Immobilization drug	$/mg	Dos mg/kg	Cost/ cow	Antagonist	$/mg	Cost/ cow	Total cost/ cow
xylazine hydrochloride (X)	$00.0064	2.2	$6.34	tolazoline (T)[a]	$00.006	$ 1.41	$ 7.74
X	$00.0064	2.6	$7.49	T	$00.135	$ 1.66	$ 9.15
X	$00.0064	3.0	$8.64	T	$00.135	$ 1.92	$10.56
ketamine hydrochloride (K)	$00.01						
X:K (4:1 ratio)		1.8:0.4	$6.98	T	$00.006	$ 1.15	$ 8.13
carfentanil citrate (C)	$10.17			naltrexone	$00.095		
X:C mixture[b]		0.4:6.7[c]	$31.79	naltrexone	$00.095	$28.50	$60.29

[a]Price based upon product available from Wildlife Pharmaceuticals, Inc. Fort Collins, Co, rather than Priscoline.We dosed at 25 mg tolagoline/100 mg xylazine. Wildlife Parmaceuticals recommends a dose of 0.5 to 1.0 mg/kg.

[b]The dosage recommend is 200 mg xylazine and 3.0 mg carfentanil per moose.

[c]The dosage listed for carfentanil is in µg/kg.

pensive, but is not approved for use in animals used for human consumption.

Carfentanil on the other hand is dangerous to humans, but provides rapid and reliable immobilization. It is more expensive per animal immobilized and antagonized than using xylazine or xylazine:ketamine mixtures. Animals antagonized with naltrexone recover rapidly (4-7 minutes) ensuring expedient processing times. As a consequence, the length of the immobilization can be controlled by the biologist and there is no waiting for an animal to recover. This is particularly important in capture operations where many animals must be processed in a day.

The new Animal Medicinal Use Clarification Act (AMDUCA) which became law in the United States on 9 December 1996 (Federal Register, Nov 7, 1996) clearly states that animals harvested as food must be considered food animals and timing of extra-label drug use must take this into account. This impacts state and federal agencies when administering drugs to moose because they must follow the guidelines that prohibit the use of these drugs during or 45 days prior to a legal hunting season. The regulation also allows biologists extra-label use under the supervision of a veterinarian.

There are tradeoffs when using any drug or drug combination for immobilization. However, we recommend using xylazine or a xylazine:ketamine mixture when immobilizing captive moose where animals can be observed easily. They can also be used for wild animals caught in wire (i.e., snares, swing sets, etc.) or in situations where human safety is paramount and rapid induction/recovery times are not essential. It is also recommended for moose in school yards or other public places where lost darts pose a public safety hazard. We do not recommend using xylazine or xylazine:ketamine in situations where there is loud noise or other external stimuli that may excite the moose.

We recommend using a carfentanil: xylazine mixture when immobilizing wild moose from helicopter or snowmachine where induction times are important. We also recommend a starting dose of 3 mg carfentanil and 200 mg xylazine for adult cows in winter. This dosage can be increased (4.5 mg carfentanil and 300 mg xylazine) for fall moose in good condition or large bulls. Induction times and level of immobilization should be used to evaluate this starting dose.

Thus far, no drug meets all the criteria outlined by Franzmann (1982) as the ideal. Choices as to which product to use when immobilizing moose must be based upon multiple criteria. Until we find a better product, both xylazine and carfentanil have a place as agents to immobilize moose.

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