The use of Ketamine-Xylazine and Ketamine-Medetomidine with and without their antagonists Yohimbine and Atipamezole Hydrochloride to immobilize Raccoons (*Procyon lotor*) in Ontario, Canada

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This study was undertaken to identify a drug combination that provided a suitable plane of anesthesia and pain suppression and reduced recovery time for minor surgical procedures in raccoons. In fall 2004, 40 wild Raccoons (*Procyon lotor*) were chemically immobilized using ketamine hydrochloride combined with either xylazine or medetomidine hydrochloride. Immobilizing treatments within and between drug types were compared in terms of induction, arousal and recovery times. The ketamine-xylazine (KX) group ($n = 20$) was given a combination of 20 mg/kg ketamine hydrochloride and 2 mg/kg xylazine hydrochloride by body weight, and the effects on induction, arousal and recovery time were recorded with and without the antagonist yohimbine hydrochloride. The ketamine-medetomidine (KM) group ($n = 20$) was given a combination of 5 mg/kg ketamine hydrochloride and 0.05 mg/kg medetomidine hydrochloride by body weight, and induction, arousal and recovery times were recorded with and without the use of the antagonist atipamezole hydrochloride. Administration of yohimbine hydrochloride at 0.1 mg/kg body weight to the KX group and atipamezole hydrochloride at 0.25 mg/kg body weight to the KM group produced considerably shorter arousal and recovery times in the KM group ($P = 0.016$). Mean arousal and recovery time with standard deviations $\pm$ (SD) for the KX group with yohimbine hydrochloride antagonist were 36.10 ± 10.69 and 94.2 ± 23.18 minutes; for the KM group with atipamezole hydrochloride antagonist, they were 7.95 ± 3.94 and 65.58 ± 14.75 respectively. At these doses, the KM combination reversed with atipamezole hydrochloride significantly reduced arousal and recovery times and resulted in a quality of anesthesia that would allow safe tooth and blood extraction in Raccoons.

Key Words: ketamine; medetomidine; xylazine; yohimbine; atipamezole; raccoon; *Procyon lotor*; chemical immobilization

Introduction

Field immobilization of wildlife using various chemical immobilizing agents has been well documented (Mech *et al.* 1965; Bigler and Hoff 1974; Gregg and Olson 1975; Deresienski and Rupprecht 1989; Belant 1991, 2005; Kreeger 1999; Gehrt *et al.* 2001). The Ministry of Natural Resources and Forestry (MNRF) wildlife research and monitoring section has an ongoing research and management program in response to rabies in multiple terrestrial carnivore species (Rosatte *et al.* 1993, 2009). This has led to the development of many research projects involving the chemical immobilization of Red Foxes (*Vulpes vulpes*), Striped Skunks (*Mephitis mephitis*) and Raccoons (*Procyon lotor*) using various tranquilizers, sedatives and dissociative anesthetic agents (Rosatte and Allan 2009; Rosatte *et al.* 2010). Immobilizing agents are necessary to allow safe handling of live-trapped animals to acquire morphological measurements, permit ear-tagging, apply a radio collar or perform minor surgical procedures such as premolar tooth extraction and blood collection. Tooth and blood collection are required to determine bait acceptance and rabies antibody level following oral rabies vaccine delivery to foxes, skunks and raccoons by hand or aircraft (Rosatte *et al.* 1993, 2010, 2011). Surgical procedures such as tooth and blood extraction require an adequate level of anesthesia, muscle relaxation and pain suppression. Ketamine alone will provide anesthesia, however muscle relaxation is dosage

dependent and pain suppression requires the addition of an analgesic (Gregg and Olson 1975; Fuller and Kuehn 1983; Dzialak *et al.* 2002). Although the analgesic promotes good muscle relaxation and pain suppression it may prolong recovery time (Dzialak *et al.* 2002). Combining ketamine with a tranquilizer or sedative has been observed to offset the convulsions often observed when using this drug and provide better muscle relaxation and analgesic properties in some wildlife species (Ramsden *et al.* 1976; Fuller and Kuehn 1983; Seal and Kreeger 1987; Dzialak *et al.* 2002; Rosatte and Allan 2009). Not all tranquilizers are reversible but recovery time can be reduced by reversing sedatives using alpha-2 antagonists. Improvements in recovery time have been observed after administering yohimbine hydrochloride to reverse the effects of xylazine in Mule Deer (*Odocoileus hemionus*), White-tailed Deer (*Odocoileus virginianus*), Elk (*Cervus elaphus*), Polar Bears (*Ursus maritimus*) and Raccoons (Jessup *et al.* 1983; Mech *et al.* 1985; Ramsay *et al.* 1985; Deresienski and Rupprecht 1989; Rosatte 2007). Ideally, field operations require the safe release of animals following immediate recovery from anesthetic, hence, the need for a drug combination that immobilizes animals safely and reduces recovery time.

Medetomidine hydrochloride is an alpha-2 agonist that is more potent and 10 times more selective than xylazine hydrochloride; it actively attaches to sites at a ratio of 1620:1 compared with 160:1 for xylazine (Sin-

clair 2003). Medetomidine hydrochloride has been administered to Coyotes *(Canis latrans)*, Red Foxes and Raccoons with reasonable success in animal handling procedures such as measurements and innoculations (Baldwin *et al*. 2008). When combined with ketamine hydrochloride, medetomidine hydrochloride has been used effectively to chemically restrain a variety of other wildlife species (Tsuruga *et al.* 1999; Haulena and Gulland 2001; Fernandez-Moran *et al.* 2001; Dzialak *et al.* 2002; Bieglböck and Zenker 2003; Fournier-Chambrillon *et al.* 2003; Belant 2005; Robert *et al.* 2012). The effects of this combination can be quickly reversed using the antagonist atipamezole hydrochloride and this procedure has demonstrated smooth induction, good immobilization and rapid recovery in Eurasian Otters, *(Lutra lutra)* European Mink (*Mustela lutreola*), Polecat (*Mustela putorius*) (Fernandez-Moran *et al.* 2001; Fournier-Chambrillon *et al.* 2003) and Raccoons (Robert *et al.* 2012). The ketamine-medetomidine combination has been reported to provide a good level of anesthesia and muscle relaxation and a better quality of surgical anesthesia than a ketamine-xylaxine combination in rabbits (Henke *et al.* 2005).

The purpose of this study was to compare KX and KM drug combinations with and without antagonists and their effects on induction, arousal and recovery times. I also evaluated which drug combination meets the pain suppression and muscle relaxation requirements during minor surgical procedures and demonstrates the shortest recovery time in Raccoons.

Methods

During the week of 6–10 September, as part of MNRF rabies research operations in the Niagara region (43°05'N, 79°05'W), Raccoons were randomly trapped using number 108 and 106 Tomahawk live traps (Tomahawk Live Trap Company, Hazelhurst, Wisconsin, USA), baited with sardines in soya oil. Animals were transported by pick-up truck and housed at the Codrington Research Facility, Codrington, Ontario, Canada (44°08'N, 77°48'W). Animals were divided into two groups of 20 animals that were similar in terms of age and sex. The KX group included four adult males, five adult females, six juvenile males and five juvenile females. The KM group included five adult males, five adult females, four juvenile males and six juvenile females. Each animal was transferred from the trap into a plywood nesting box (60 cm × 58 cm × 30 cm) with access to an individual wire cage holding pen (152 cm × 60 cm × 60 cm) and allowed to acclimatize for 1 week before treatment. Raccoons were fed 170 grams per day of fox maintenance feed, (Martin Mills Inc., and Elmira Ontario, Canada) and provided with water on a daily basis. Animals were not fed on the morning of the experiment and feeding was postponed until all animals had recovered fully from the anesthetic. Raccoons were captured in their nesting boxes using a

4-foot snare pole (Ketch-all San Luis Obispo, California USA) and placed into a Tomahawk 108 live trap and weighed to the nearest tenth of a kilogram minus the trap weight. Mean ambient air temperature was calculated using hourly data from Environment Canada from 1000 to 1600 EST (Environment Canada 2014) which included the time frame of the treatments.

Treatment one commenced on 20 September 2004. The KX group was immobilized using a 10:1 ratio of the two drugs by body weight: 20 mg/kg ketamine hydrochloride (Rogarsetic 50 mL, 100 mg/mL, Pfizer Canada Inc., Pointe-Claire, Quebec, Canada) and 2 mg/kg of xylazine hydrochloride (Anased 50 mL, 100 mg/mL, Novopharm Ltd., Toronto, Ontario, Canada). Raccoons were restrained in their nesting boxes using a plunger squeeze technique and given an intramuscular injection into the quadriceps muscle of the hind limb using a handheld 3 mL syringe with 22 gauge needle. Mean ambient air temperature was 19.8°C.

On 21 September 2004, the KM group was immobilized 100:1 ratio of the two drugs by body weight; 0.05 mg/kg ketamine hydrochloride and 0.050 mg/kg medetomidine hydrochloride (Domitor, 10 mL, 1.0 mg/mL, Novartis Animal Health Canada Inc. Mississauga, Ontario, Canada). Mean ambient air temperature was 23.9°C.

Treatment two began on 5 October 2004 with the KX group receiving the same drug combination as in the first treatment. Approximately 18 minutes post-induction the animals received the antagonist yohimbine hydrochloride (Lloyd Yobine, 20 mL, 2 mg/mL (Teva Canada, Scarborough, Ontario, Canada) at a dosage of 0.1 mg/kg. Mean ambient air temperature was 10.1°C

On 6 October 2004, the KM group was immobilized using the same dose as in the first treatment followed by intramuscular injection of the antagonist atipamezole hydrochloride (Antisedan, 10 mL, 5.0 mg/mL, Novartis Animal Health Inc.) at a dose of 0.25 mg/kg 18 minutes post-induction. Mean ambient temperature was 16.4°C.

Injection, induction, arousal and recovery times were recorded for individual animals in each group. Injection time was recorded as the time following injection: induction time was measured as the time following injection to lack of responsiveness to tactile stimuli (palpebral reflex and toe pinch). Arousal time was recorded as time from induction to the animal's first attempt to raise its head from the floor of the holding pen. Recovery time was recorded as the time from arousal to lack of ataxia in the hind limbs. Antagonists were injected on average 18 minutes after induction to simulate the length of a minor surgical procedure. All animals were handled according to MNRF Animal Care Committee protocol #04-91.

Data analysis

Induction, arousal and recovery times were entered into Excel (windows version 2000, Microsoft, Red-

mond, Washington, USA) and exported into Statistica® version 6.0 (Statsoft, Tulsa, Oklahoma, USA). Before analysis, log transformation of all data was completed to establish normality and achieve homogeneity of variances. Data for one animal from the KM group were excluded during analysis as normality could not be attained because of an overly long recovery time. Differences in induction, arousal and recovery times were tested within and between drug combinations for the two treatments. A MANOVA was used to detect differences within and between the KX and KM groups. Differences between age and sex classes were not examined as sample sizes were considered too small, i.e., low power increased the chance for Type II error (Zar 1999). Mean value statistics, standard deviation and range for each group were calculated. Alpha was set at $P = 0.05$.

Results

Analysis of covariance showed that body weight had no significant effect on induction, arousal or recovery time ($P > 0.05$).

During treatment one, when no antagonist was used and comparisons between induction, arousal and recovery times were made between the KX and KM drug types, shorter induction, arousal and recovery times were observed for the KX drug combination ($F_{(2, 76)} = 7.31$, $P = 0.001$).

In treatment two, when antagonists were used, induction time for the KX group was twice as long as in treatment one ($P = 0.026$). Arousal and recovery times were significantly shorter following administration of yohimbine hydrochloride ($P < 0.001$ and $P = 0.015$) respectively and significant differences were found for induction, arousal and recovery times when comparing treatments within the KX group ($F_{(2,76)} = 10.74$, $P < 0.001$). For the KM group, when the antagonist atipamezole hydrochloride was used, shorter arousal and recovery times were observed compared with treatment one ($P < 0.001$) with no differences observed between induction times, and significant differences were observed between treatments for induction, arousal and recovery times ($F_{(2, 74)} = 22.72$, $P < 0.001$).

Comparing drug combinations, no significant differences were observed regarding induction time. Raccoons in the KM group demonstrated significantly shorter arousal and recovery times when given atipamezole hydrochloride compared with those in the KX group given yohimbine hydrochloride ($F_{(2, 74)} = 4.354$, $P = 0.016$). Differences in induction, arousal and recovery times within and between drug combinations are shown in Table 1.

Discussion

Variation in the length of induction time to induce anesthesia in raccoons was observed in the KX group between treatments. Poor induction may be attributed to the behavior of individual animals before immobilization and may be attributable to various biological or behavioural influences. Some animals were very calm during injection while others displayed aggression. Animals were restrained in nesting boxes by quickly lifting the lid and pinning the Raccoon using a plunger type squeeze technique. Although Raccoons were often restrained quickly, more aggressive animals took longer to restrain. Prolonged restraint coupled with the aggressive and agitated state of these animals may be the reason for some of the variation observed in induction times between the two treatments in the KX group. Aggressive behavior has been known to affect drug absorption and result in failure to achieve optimum sedation (Sinclair 2003). Because I did not record animal behavior for every injection I cannot say whether aggressive behavior affected induction time in the KX group.

Repeated exposure to drugs is thought to prolong induction and recovery times in some mammals. This has been observed in seals and raccoons, where repeated exposure to ketamine and medetomidine increased induction time (Field *et al.* 2002; Wheatley *et al.* 2006; Robert *et al.* 2012). In this study, an increase in induction during the second KX treatment was observed; however, no significant difference in induction time was observed in the KM group. Although the increased induction time in the KX group might be a result of drug tolerance, it could also be related to other biological or ambient conditions.

A study in Quebec observed longer induction time for Raccoons administered KM in the fall, indicating lower ambient temperature and increased body fat may affect drug absorption at this time of year (Baldwin *et*

TABLE 1. Induction, arousal and recovery times of Raccoons (*Procyon lotor*) administered ketamine hydrochloride combined with either xylazine hydrochloride or medetomidine hydrochloride without and with the antagonists yohimbine hydrochloride and atipamezole hydrochloride respectively.

Drug combination	n	Induction time mean ± SD (range)	Arousal time mean ± SD (range)	Recovery time mean ± SD (range)
KX without YH	20	3.6 ± 2.54 (1–10)	55 ± 16.06 (28–95)	113.65 ± 26.41 (73–160)
KX with YH	20	6.25 ± 4.84 (2–19)	36.10 ± 10.69 (18–60)	94.2 ± 23.18 (61–145)
KM without AH	19	6.74 ± 3.81 (2–18)	71.73 ± 24.23 (43–147)	132.1 ± 37.24 (75–201)
KM with AH	19	7.63 ± 4.68 (2–17)	7.95 ± 3.94 (3–15)	65.58 ± 14.75 (37–99)

Note: AH = atipamezole hydrochloride, SD = standard deviation, YH = yohimbine hydrochloride.

al. 2008; Robert *et al.* 2012). In my study, the mean ambient temperature was almost 10°C cooler during the second treatment which might explain the much longer induction time observed in the KX group. Mean ambient temperature differences for the KM group was 7.5°C and no differences in induction time were observed between treatments in that group suggesting that there may be a temperature threshold that delays induction however this was beyond the scope of this study.

Larger body mass has been known to cause slower induction and recovery times in the North American Porcupine (*Erethizon dorsatum*) (Morin and Berteaux, 2003); however, based on the analysis of covariance in this study, weight had no impact on induction, arousal or recovery times in Raccoons. The restraining technique used in this study provided clear access to the quadriceps muscle allowing a good site for intramuscular injection. Therefore differences in induction time are not likely attributable to faulty injection. Thus reasons for the differences in induction between treatments in the KX group remain unclear.

In the absence of an antagonist, KX allows shorter induction, arousal and recovery times than KM in Raccoons. This has also been observed in Alpine Marmots (*Marmota marmota*) where induction times were not significantly different, but arousal and recovery times were significantly longer in the KM group (Bieglböck and Zenker 2003).

For the KX group in this study, shorter arousal and recovery times were expected following intramuscular injection of the antagonist yohimbine hydrochloride. Xylazine attaches to the presynaptic adrenoreceptors, reducing the release of norepinephrine. Yohimbine reverses the xylaxine hydrochloride at the presynaptic adrenoreceptors, thus increasing the release of norepinephrine (Langer 1980; Kreeger *et al.* 1987). Reversing the effects of xylazine hydrochloride with yohimbine via intramuscular, sublingual or intravenous administration has been observed to reduce recovery times in a number of mammalian species (Jessup *et al.* 1983; Mech *et al.* 1985; Ramsay *et al.* 1985; Kreeger *et al.* 1987; Deresienski and Rupprecht 1989; Rosatte 2007). Although sublingual, femoral or jugular intravenous injection may be feasible in larger mammals, it is less desirable in operations involving large numbers of meso-carnivores where veins are smaller and where intramuscular injection is more practical (Rosatte *et al.* 2009).

Medetomidine hydrochloride induces sedation for up to 70–90 minutes when administered intramuscularly at doses of 0.03 mg/kg by weight in dogs and cats. Higher doses > 0.080 mg/kg will not increase sedation, but will prolong recovery (Sinclair 2003). In my study, drug dosages of 0.05 mg/kg medetomidine hydrochloride and 5 mg/kg ketamine hydrochloride were used on Raccoons and sedation periods averaged 124.36 minutes without administration of the antagonist atipamezole hydrochloride. Longer recovery times averaging 199.4 minutes were observed in the Fisher (*Martes pennanti*) using slightly higher doses of medetomidine hydrochloride (0.07 mg/kg) and lower ketamine hydrochloride doses averaging 3.7 mg/kg for males and 3.6 mg/kg for females (Dzialak *et al.* 2002). In the absence of an antagonist, perhaps a lower dose of medetomidine hydrochloride could be considered for non-surgical operations to reduce recovery periods in Raccoons and Fishers.

Reversing the KM drug combination using atipamezole hydrochloride resulted in shorter arousal and recovery times for Raccoons in this study. Similar results have been observed in Polar Bears, Sika (*Cervus Nippon*), Eurasian Otter, European Mink, European Polecat and Raccoons (Cattet *et al.* 1997; Tsuruga *et al.* 1999; Fernandez-Moran *et al.* 2001; Fournier-Chambrillon *et al.* 2003; Robert *et al.* 2012). This was expected as atipamezole hydrochloride fully antagonizes the sedative and behavioural effects of medetomidine hydrochloride when administered at four to six times the medetomidine hydrochloride dose (Sinclair 2003). In this experiment, medetomidine hydrochloride antagonized at five times the atipamezole hydrochloride dosage (0.25 mg/kg) and Raccoons were walking shortly after arousal but demonstrated limb ataxia likely attributable to the residual ketamine. Ketamine hydrochloride has no known antagonist. Although administering yohimbine hydrochloride has been reported to shorten arousal times in the Gray Wolf (*Canis lupus*) and Domestic cat (*Felis catus*), no improvement was observed in walking times (Hatch *et al.* 1983; Kreeger and Seal 1986*a*; Kreeger and Seal 1987). The shorter arousal times observed in the KM group may be attributed to the lower dose of ketamine (5mg/kg compared with 20mg/kg in the KX group) and the intramuscular administration of atipamezole hydrochloride. Given that yohimbine hydrochloride shortens arousal time in wolves and cats, and atipamezole hydrochloride is also an alpha-2 antagonist, it is likely that the atipamezole hydrochloride is stimulating the nervous system of Raccoons in a similar manner and contributing to shorter arousal times in the KM group.

The KM drug combination requires significantly less ketamine hydrochloride than the KX drug combination for the chemical immobilization of Raccoons. Given that ketamine is a restricted drug in Canada, lower volumes are more likely to be approved and are easier to track and maintain by the biologist. KM has been used successfully in live-animal capture programs in MNRF rabies control programs. In large-scale field operations, we successfully immobilized and performed minor surgical procedures on over 1200 Raccoons and Striped Skunks using 550 mL of ketamine, averaging less than 0.5mL of ketamine per animal (Rosatte *et al.* 2009). For the same number of animals, we would have used four times the volume of ketamine if it was

combined with xylazine hydrochloride, a difference of $1300 in cost of ketamine alone.

KM and the antagonist atipamezole hydrochloride is a better drug combination for reducing recovery in Raccoons compared with KX antagonized with yohimbine hydrochloride. No mortalities or adverse reactions were observed indicating that the drugs are safe at these doses. Smooth induction, good muscle relaxation, rapid arousal and recovery combined with a wide safety margin make KM a good replacement for KX for performing tooth and blood extraction procedures on Raccoons.

Acknowledgements

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