Received: 17 January 2023 | Revised: 16 June 2023 | Accepted: 13 August 2023

DOI: 10.1111/vec.13357

Journal of Veterinary Emergency and Critical Care

WILEY

ORIGINAL STUDY

Evaluation of the use of intranasal atipamezole to reverse the sedative effects of xylazine in dogs

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Results were presented at ACVECC VetCOT Trauma & Critical Care Symposium in 2021, Las Vegas, Nevada.

Funding information
WCVM Internship Research Fund

Abstract

Objective: To assess the ability of intranasal atipamezole to reverse sedative effects of xylazine in dogs.

Design: Prospective proof-of-concept study.

Setting: University research laboratory.

Animal: Six healthy, staff-owned dogs.

Interventions: Dogs were sedated with 1.1 mg/kg of xylazine intravenously. The sedation score of each dog was recorded every 5 minutes until they achieved a sedation score of >13/21 for 3 readings. Once achieved, 0.3 mg/kg of atipamezole was administered intranasally using a mucosal atomization device. Sedation scores continued to be recorded every 5 minutes until successful reversal was achieved (<4/21).

Measurements and Main Results: Average times to standing and normal wakefulness after administration of intranasal atipamezole were 6 minutes, 30 seconds and 7 minutes, 20 seconds, respectively.

Conclusions: Intranasal atipamezole successfully reversed the sedation effects of xylazine. The findings of this study provide justification for future controlled prospective studies into the potential use of intranasal atipamezole in a variety of settings including exposure to xylazine in operational canines as well as bioavailability studies for optimal dosing.

KEYWORDS
accidental drug exposure, alpha-2 agonist, drug intoxication, Illicit drugs, operational canine, toxicology, working dog

1 | INTRODUCTION

Xylazine is an alpha-2-adrenergic receptor agonist that is approved for use in veterinary medicine as a sedative drug. Xylazine has increasingly been documented as an adulterant additive in drugs of abuse in Puerto Rico, the United States, and Canada.[1–4] Documented cases remained limited until the early 2020s when news reports surrounding xylazine-associated overdose deaths in people surged across North America.[4–6] Operational canines are working dogs that serve as involuntary nonhuman officers in various capacities from military and law enforcement to humanitarian aid.[7] Operational canines play vital roles in detection of illicit substances due to their training and keen sense of smell and are put at risk of intoxication, both orally and through inhalation, by pharmacologically active substances through their work.[7]

Xylazine is an alpha-2 agonist that is infrequently used in dogs and cats at the time of writing, having been largely replaced by more

Abbreviation: CNS, central nervous system.

modern drugs in the same class such as dexmedetomidine for sedation and anesthetic premedication. Alpha-2 agonists produce cardiovascular effects such as bradycardia, associated first- and second-degree heart block, reduction in cardiac output, and peripheral vasoconstriction resulting in increased systemic vascular resistance.[8] Nervous system effects are characterized by central nervous system (CNS) depression.[8] Other systemic effects include thermoregulatory disruption and the potential for emesis after parenteral administration.[8] Though data pertaining to the bioavailability in dogs after oral or intranasal administration of xylazine are not available, the lipid-soluble substance appears to be readily absorbed through either route in humans based on evidence from case studies following intentional or accidental xylazine exposure and overdose in people.[9,10] The cardiovascular, CNS, and thermoregulatory effects of xylazine and other alpha-2 agonists are easy to manage when these drugs are used clinically as part of multimodal anesthesia but could be dangerous or even fatal when larger doses are acquired accidentally outside of a clinical environment.[11]

Intranasal naloxone is used by first responders, including handlers of operational canines in law enforcement, to reverse known or suspected exposure to opioids in the field with minimal training required for successful delivery of the intranasal product. Since naloxone does not reliably reverse the effects of xylazine, an effective, safe, and easily administered alpha-2 reversal agent is needed to manage the risk of exposure to xylazine for operational canines in the field.[12]

The alpha-adrenergic receptor antagonists atipamezole and yohimbine are currently labeled in North America for use in veterinary medicine as reversal agents for alpha-2 agonist sedatives. Of the 2, atipamezole is generally considered superior due to its high selectivity for alpha-2 receptors, wide therapeutic index, and product availability in the North American veterinary drug market. At the time of writing, atipamezole is unavailable for use outside of veterinary clinical environments and is labeled for intramuscular injection only, making it generally inaccessible for use by handlers of operational canines who are not trained to use injectable products on their dogs. Since handlers of operational dogs are familiar with the use of naloxone as an intranasally administered product in the field, providing xylazine reversal intranasally would improve safety and efficacy of reversal protocols following suspected canine drug exposure.

The use of intranasal medications in dogs is not clinically novel. Intranasal naloxone is successfully used to reverse opioid toxicities in dogs, and intranasal midazolam has been administered with the use of a mucosal atomization device to treat seizures in dogs.[12,13] There is evidence of successful intranasal use of reversal agents for alpha-2 agonists in several exotic species and in white-tailed deer, with no existing studies demonstrating intranasal use of these products in dogs.[14–18] The objective of this study was to evaluate, using a validated sedation score, the feasibility of using intranasally administered atipamezole to reverse xylazine-induced sedation in dogs.

2 | MATERIALS AND METHODS

This study was approved by the University of Saskatchewan's Animal Research Ethics Board (20200109). Six staff-owned dogs were recruited from the institution, and owner consent was obtained. Inclusion criteria for subjects were mesocephalic dogs between 1 and 7 years of age, 20–40 kg in weight, not on any medications, and systemically healthy. A sedation score previously validated by Wagner et al was chosen as a guideline for this study (Table 1).[3]

Participating dogs were fasted for a minimum of 8 hours prior to data collection. The study was conducted over 2 consecutive days and dogs were assigned to a study day based on owner convenience. On the day of data collection, subjects were weighed, examined by a veterinarian, and had baseline packed cell volume, total plasma protein, blood glucose[a], and blood urea nitrogen[b] measured prior to study commencement. All 6 dogs enrolled were determined to be healthy and were included in the study. To begin, an intravenous catheter was placed in a cephalic vein. Prior to xylazine administration, a baseline sedation score was measured. Immediately thereafter, 1.1 mg/kg of xylazine[c] was administered intravenously through the catheter and a timer was started. Vital signs and sedation score were recorded every 5 minutes following the administration of xylazine. Supplemental flow-by oxygen was provided when tolerated by the dogs, and eye lubrication[d] was applied OU every 15 minutes to prevent the formation of corneal ulcers. Once a sedation score of greater than or equal to 13/21 was obtained for 3 consecutive measurements, 0.3 mg/kg of atipamezole[e] was administered intranasally using a 3-mL syringe[f] with a mucosal atomization device.[g] Efforts were made to administer ½ of the total volume of atipamezole into each nostril. A score of >13/21 was defined as sedated, and a successful sedation reversal was defined as a score of <4/21.[3]

Atipamezole was available to be administered for reversal by intramuscular injection if sedative effects were maintained beyond 45 minutes following intranasal reversal. Once the desired reversal score was reached, the timer was stopped, and the IV catheter was removed. Dogs were held in kennels for observation for 1–2 hours following catheter removal and released to owners later the same day. Approximately 24 hours after study participation, a follow-up contact was made with owners of participating dogs to establish their status and inquire about any observed adverse effects.

2.1 | Statistical methods

Descriptive statistics were used to illustrate findings. Normality of outcomes was assessed visually with a histogram and tested with a Shapiro–Wilk test. Normality assessment was carried out with a commercial statistics package.[h] Means and standard deviations were calculated with analysis tools in a commercial database program[i] and reported for time elapsed from atipamezole administration to normal wakefulness; standing; and nonsedated score.

TABLE 1 Sedation scale, adapted from Wagner et al.[3]

Category	Description	Score
1. Spontaneous posture	○ Standing	0
	○ Tired but standing	1
	○ Lying but able to rise	2
	○ Lying but difficulty rising	3
	○ Unable to rise	4
2. Palpebral reflex	○ Brisk	0
	○ Slow but with full corneal sweep	1
	○ Slow but with ownly partial corneal sweep	2
	○ Absent	3
3. Eye position	○ Central	0
	○ Rotated forward/downward but not obscured by third eyelid	1
	○ Rotated forward/downward and obscured by third eyelid	2
4. Jaw and tongue relaxation	○ Normal jaw tone, strong gag reflex	0
	○ Reduced tone, but still moderate gag reflex	1
	○ Much reduced tone, slight gag reflex	2
	○ Loss of jaw tone and no gag reflex	3
5. Response to noise (handclap)	○ Normal startle reaction (head turn toward the noise/cringe)	0
	○ Reduced startle reaction (reduced head turn/minimal cringe)	1
	○ Minimal startle reaction	2
	○ Absent reaction	3
6. Resistance when laid into lateral recumbency	○ Much struggling, perhaps not allowing this position	0
	○ Some struggling, but allowing this position	1
	○ Minimal struggling/permissive	2
	○ No struggling	3
7. General appearance/attitude	○ Excitable	0
	○ Awake and normal	1
	○ Tranquil	2
	○ Stuporous	3

3 | RESULTS

Six dogs were included in this study. The age range was 1–7 years. Breed distribution included 1 Husky, 1 Australian Cattle Dog mix, 1 Queensland Blue Heeler mix, 1 Labrador Retriever, and 2 Labrador Retriever mixes. There were 4 neutered females and 2 neutered males.

The average starting sedation score was 1.33/21 (range 1–3/21). The average time from xylazine administration to a sedation score of 13/21 was 8 minutes ± 2 minutes, 27 seconds in 5 out of 6 dogs. One dog never reached a sedation score of 13/21 and was assessed to be at peak sedation with a score of 12/21, 15 minutes after xylazine administration. In this subject, sedation scores were monitored for a total of 45 minutes after xylazine administration (sedation score 10/21) before the atipamezole was administered intranasally. Table 2 lists individual subjects scores and Figure 1 demonstrates the changes in sedation scores for each animal over time.

After intranasal atipamezole administration, the mean time to normal wakefulness was 7 minutes 20 seconds ± 4 minutes 2 seconds (Category 7 General appearance/attitude = 1), time to standing was 6 minutes 30 seconds ± 3 minutes 41 seconds (Category 1 Spontaneous posture = 0), and time to nonsedated score was 12 minutes 20 seconds ± 6 minutes 33 seconds (Total score <4/21) (Table 1). The data were found to be normally distributed. None of the dogs required an intramuscular rescue dose of atipamezole. The vital parameters measured during the study for all dogs are included in a supplemental table.

Dogs were observed post-data collection and owners were questioned the following day for evidence of pawing, sneezing, coughing, or epistaxis. None of these clinical signs were observed in any of the dogs involved in this study. One dog developed regurgitation that required treatment approximately 3 hours following recovery.

TABLE 2 Sedation scores and time to sedation endpoints.

Dog	Presedation score	Sedation score at intranasal atipamezole administration (out of 21)	Time of atipamezole administration from administration of xylazine (min)	Time from atipamezole administration to tired but standing (min)	Time from atipamezole administration to normal wakefulness (min)	Time from atipamezole administration to score <4/21 (min)
1	1	15	26	14	14	14
2	1	14	33	2	2	2
3	1	10	45	5	5	5
4	3	15	24	6	11	11
5	1	17	23	7	7	7
6	1	13	35	5	5	10

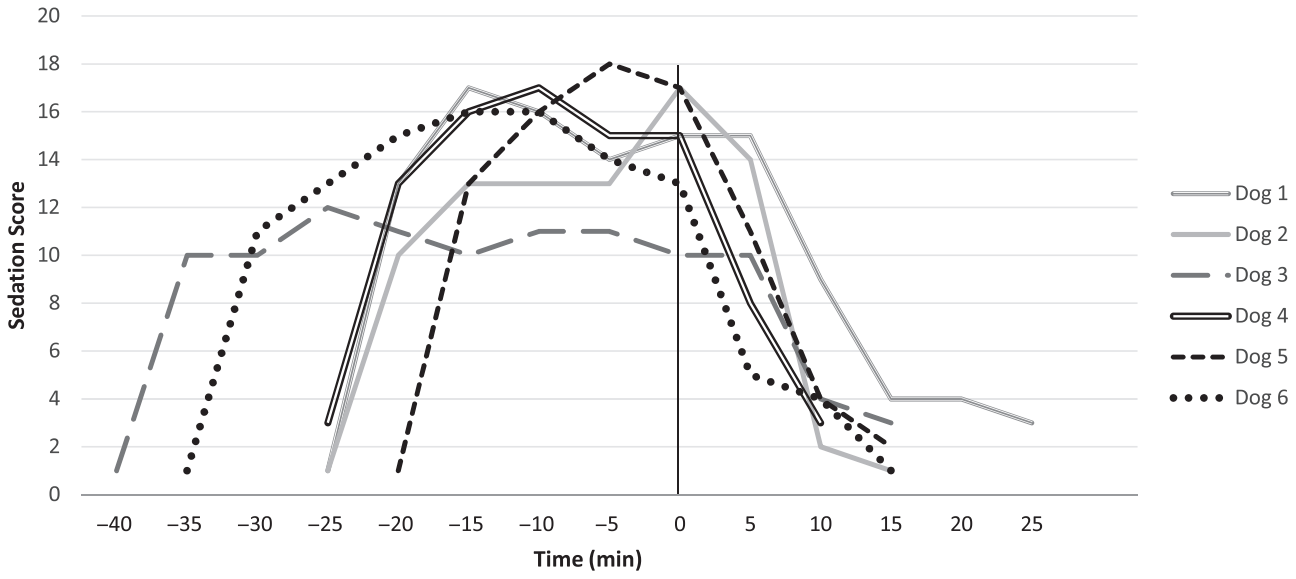

FIGURE 1 Sedation scores by time for 6 canine subjects. Atipamezole was administered at time "0."

4 | DISCUSSION

This study demonstrated effective reversal of xylazine sedation following intranasal administration of atipamezole in healthy dogs. Individual variations were noted between subjects in terms of presedation score, score at peak sedation level, and score at complete reversal.

While the use of xylazine in veterinary medicine is decreasing for small animals, its appearance in illicit drugs appears to be increasing. Dogs are at risk of being exposed to it whether they are working as operational drug-detection canines, living alongside owners who use illicit drugs, or encountering these substances while out for a walk or roaming in their community. Due to the cardiovascular and respiratory effects of alpha-2-adrenergic receptor agonists like xylazine, unintentional and uncontrolled exposure through inhalation or ingestion could have life-threatening consequences. When used in clinical settings, xylazine has been found to produce patient recumbency for approximately 50 minutes, and patients remain ataxic for up to 165 minutes.[19] In a study evaluating the use of intramuscular atipamezole to reverse xylazine, authors found the mean time for dogs to stand after atipamezole injection was 12 ± 2 minutes, 30 seconds.[19] Patients in the present study stood without ataxia an average of 6 minutes, 30 seconds (±3 minutes, 41 seconds) following intranasal administration of atipamezole, suggesting that this route of administration is not only clinically effective but also rapid in comparison to on-label dosing methods.

In both human and veterinary medicine, various pharmaceuticals are regularly administered intranasally. This mode of drug delivery is ideal for compounds that do not demonstrate good bioavailability by other routes of administration, because they are vulnerable to breakdown in the gastric environment, are absorbed poorly in the intestines, or undergo extensive first-pass metabolism in the liver. The nasal mucosa is highly vascular, allowing for rapid absorption of the drug product while also avoiding gastric breakdown or elimination via first-pass hepatic metabolism.[20,21] Atipamezole is a small-molecular-weight, lipid-soluble compound and these properties indicate the potential for successful absorption following

intranasal administration.[22,23] Additionally, intranasal drug administration requires minimal training and practice, and avoids potential needle injury to recipient or administrator during emergencies. Handlers of operational canines are already trained to administer intranasal medications like naloxone to both people and animals, making this an easily transferrable route of administration for other drugs. With the fast reversal times found in the present study, it is expected that further administration of atipamezole by injection following an intranasal reversal dose would be unnecessary for typical healthy dogs.

There are no studies in dogs dedicated to evaluating the side effects of intranasal drug administration in dogs. In people, documented adverse side effects following intranasal drug administration include nasal dryness, irritation, congestion, sneezing, and nasal itching. Extrapolating these side effects to subjects in the present study, dogs were observed post-data collection and owners were questioned the following day for evidence of pawing, sneezing, coughing, or epistaxis and none were seen. One dog developed regurgitation that required treatment approximately 3 hours following recovery, but the significance of this complication was not apparent due to a small sample size and no gastrointestinal side effects observed in other subjects. The administration of the intranasal atipamezole was easy to perform, likely because the dogs were sedated. A previous study reported difficulty administering intranasal midazolam in 45% of dogs due to sneezing and erratic motion in animals experiencing active seizures.[13] These challenges suggest that clinical application of this route of administration is most useful in sedate or otherwise moribund dogs.

For this study, we used a previously validated sedation score to objectively quantify patient sedation levels. However, using this scale with dogs only sedated with xylazine had several limitations. First, animals sedated with an alpha-2-adrenergic receptor agonists alone are very sound and touch sensitive.[11] Assessing response to auditory stimulation through a handclap test was effective and produced reliable arousal in most dogs. Since this parameter was assessed prior to "resistance when laid into lateral recumbency," we found that dogs often had increased resistance to being placed in lateral recumbency, which skewed assessment of this parameter. Performing auditory stimulation last would have been a more effective way to ensure each assessment was evaluated independently and not influenced by response to previous parameters. Additionally, while the score for "normal wakefulness" dictated by Wagner et al was 2/21, some dogs demonstrated what our team assessed as "clinically awake" at a score of 3/21, correlating to "tired but standing," "some struggling but allowing [being placed into lateral recumbency]," and "awake and normal."[3] The investigators determined the 2 clinically relevant endpoint observations, based on interpretation of Wagner et al's sedation score, to be "time to tired but standing" (spontaneous postures) and "time to awake and normal" (general appearance/attitude).[3] These clinical modifications to our protocol conflicted with the previously set parameters for sedation score requirements and highlight the need for either (i) modifications to the sedation score; (ii) modifications to the assessment parameter order; or (iii) alterations to the definition of sedation accounting for individual responses to alpha-2 sedation.

Limitations to this study include small sample size with only 6 dogs being included and no control group. The optimal dose and the bioavailability of intranasal atipamezole were not evaluated, and investigators were not blinded to the timing of atipamezole administration. Given the use of xylazine as a sole sedative, dogs were sound and touch sensitive, which led to previously mentioned challenges with the order of assessments to score sedation for subjects in this study. Finally, performing sedation assessments every 5 minutes was perceived to be a longer interval than ideal, due to depth of sedation changing quickly and being inaccurately illustrated with measurements taken this far apart. There was also 1 dog that did not reach the desired sedation score and remained arousable with a maximum sedation score of 12/21. As xylazine works rapidly when administered IV, sedation scoring every 3 minutes or less to accurately observe and record all clinical changes would improve accuracy of quoted intervals to maximum sedation following xylazine administration and to full reversal following atipamezole administration.

The findings of this study suggest a need for controlled prospective studies exploring the use of intranasal atipamezole in a variety of settings. We conceptualized this study originally with operational canines in mind, and given the ubiquitous use of alpha-2 agonists for sedation in small animal veterinary practice, the findings here could be transferrable to other clinical contexts, particularly in high-volume practice settings where risks of errors following injectable administration could be increased. Future studies should investigate effective doses of alpha-2 reversal agents for intranasal administration with the goal of providing safe and effective alternative dosing routes for these widely used alpha-2 agonists like dexmedetomidine. Side effects to be investigated should include disruption of canine olfaction so that handlers know what to expect in their canine partner's performance following administration of intranasal atipamezole. Access to intranasal atipamezole has exciting implications for reversing accidental exposure and clinical use of xylazine in dogs. Effective and safe administration of intranasal atipamezole in dogs could also provide a model for analogous use of this reversal agent in humans, which could improve the ability of first responders to save the lives of overdose patients exposed to xylazine in the field.

AUTHOR CONTRIBUTIONS

Alex P. Focken: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; writing—original draft; writing—review and editing. **Jordan M. Woodsworth**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; writing—original draft; writing—review and editing. **Jennifer M. Loewen**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING INFORMATION

This study was supported by the WCVM Internship Research Fund. None of the authors of this article have a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

OFFPRINTS

No offprints will be provided.

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ENDNOTES

[a] AlphaTrak; Zoetis, Kalamazoo, MI.
[b] Azostix; Siemens Medical Solutions, Tarrytown, NY.
[c] Rompun; Bayer Inc., Mississauga Ontario, Canada.
[d] Optixcare; Aventix Animal Health Corp, Burlington, Ontario, Canada.
[e] Antisedan; Zoetis Canada Inc., Kirkland, Quebec, Canada.
[f] BD, Franklin Lakes, NJ.
[g] Teleflex Medical, Morrisville, NC.
[h] STATA 17. Stata Statistical Software: Release 17; StataCorp LLC, College Station, TX.
[i] Excel 365 2016; Microsoft 365 Redmond, WA.

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How to cite this article: Focken AP, Woodsworth JM, Loewen JM. Evaluation of the use of intranasal atipamezole to reverse the sedative effects of xylazine in dogs. *J Vet Emerg Crit Care*. 2024;34:57–62. https://doi.org/10.1111/vec.13357