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RESEARCH ARTICLE

A Comparison of Anesthetic and Cardiorespiratory Effects of Tiletamine-Zolazepam/Xylazine and Tiletamine-Zolazepam/Xylazine/Tramadol in Dogs

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ABSTRACT

This study compared the anesthetic and cardiorespiratory effects of 3 intramuscular anesthetic combinations in 8 dogs. Tiletamine-zolazepam (8 mg kg^{-1}) and xylazine (0.5 mg kg^{-1}) (TZX); Tiletamine-zolazepam (8 mg kg^{-1}), xylazine (0.5 mg kg^{-1}) and tramadol (2 mg kg^{-1}) (TZXT); or the TZXT protocol plus atipamezole (0.05 mg kg^{-1}) given 30 min later to reverse xylazine, were administered. Immobilization and analgesia scores of the dogs and baseline physiological parameters (heart rate, respiratory rate, non-invasive systolic, diastolic and mean arterial blood pressures, arterial hemoglobin oxygen saturation, and rectal temperature) were determined. All 3 combinations effectively induced anesthesia, and dogs became laterally recumbent within 5 min. The changes in physiological parameters after administration of the drug combinations remained within biologically acceptable limits. While both TZX and TZXT appeared to be effective injectable anesthetic combinations, TZXT provided significantly better analgesia with a longer duration than did TZX. Atipamezole administration provided effective antagonism and no adverse effects were observed in this study.

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INTRODUCTION

Pre-anesthetic medications play an important role in safe anesthesia management. When used appropriately, these medications induce a desirable state of calm or sedation (Vesal *et al.*, 2011). Several drugs or drug combinations are used for this purpose, and it is known that some drug combinations using low doses of each drug produce more reliable hypnosis or sedation than a higher dose of each drug alone (Vettorato and Bscco, 2011). Tiletamine-zolazepam has been used alone or in combination with other anesthetic agents in dogs (Krimins *et al.*, 2012), and one particular combination, tiletamine-zolazepam and xylazine (TZX), has been widely used in dogs (Jang *et al.*, 2004). With advances in alpha-2 agonist development, xylazine is now less commonly used in animals and has gradually been replaced by medetomidine (Silva *et al.*, 2007; Kalhoro and Memon, 2011). However, in many countries, medetomidine cannot be used in veterinary medicine because of technical, economic, and legal restrictions. Thus, TZX is an alternative injectable combination in dogs.

Tramadol is a centrally acting analgesic with several mechanisms of action, acts as a weak μ-opioid agonist coupled with inhibition of synaptic reuptake of serotonin and norepinephrine to achieve spinal modulation of pain. Tramadol has been studied in dogs (Choi *et al.*, 2011) and it is reasonable to assume that TZX combined with tramadol (TZXT) would result in an injectable anesthetic protocol with rapid onset of anesthesia and effective analgesia in dogs, but to the authors' knowledge, there are no published data available regarding the use of tramadol in combination with TZX in dogs.

An antagonist may be required when anesthetized animals show profound depression of vital signs, adverse effects of the given anesthetics, and/or delayed recovery from anesthesia. Atipamezole is the most selective and potent antagonist of central and peripheral alpha-2-adrenoceptors, increases HR and blood pressure, causes central nervous system stimulation (Rioja *et al.*, 2008). Atipamezole reverses the sedative, cardiovascular, and analgesic effects of xylazine in a several animal species (Dematteis *et al.*, 2008). Although there are many studies available about atipamezole antagonism of medetomidine

in dogs (Ko *et al.,* 2007), there have been few published reports about atipamezole antagonism of xylazine in dogs (Talukder *et al.*, 2009).

The objectives of this study were to evaluate and compare the anesthetic and cardiorespiratory effects of TZX and TZXT in dogs. It was hypothesized that TZXT would have a longer duration of anesthesia and provide a better quality of analgesia than TZX. It was further hypothesized that administration of atipamezole 30 min after administration of TZXT would shorten recovery time without affecting recovery quality.

MATERIALS AND METHODS

This study was conducted under the guidelines provided by the Animal Care and Use Committee of the Northwest A&F University. All dogs were determined to be in good physical condition based on physical examination and complete blood count. Eight mongrel dogs (4 females and 4 males) were used in the crossover study. The mean age of the dogs was 15.5 (range 12–17) months and the mean body weight was 11.5 (range 9.6-13.7) kg. Food, but not water, was withheld for 6 hours prior to the start of the experiment. Each animal was allowed to acclimatize to a room with temperature at 25°C for at least 30 min before each experiment was commenced. Subsequently, animals were leashed and weighed. Three IM drug combinations were administered to the dogs in random order:

- TZX: Tiletamine-zolazepam (Zoletil 100, Virbac Corporation, France) 8 mg kg^{-1} and xylazine (Rompun, Bayer, Germany) 0.5 mg kg^{-1}.
- TZXT: Tiletamine-zolazepam 8 mg kg^{-1}, xylazine 0.5 mg kg^{-1}, and tramadol (Tramal 100; Grunenthal GmbH, Germany) 2 mg kg^{-1}.
- TZXTA: Tiletamine-zolazepam (8 mg kg^{-1}), xylazine (0.5 mg kg^{-1}), and tramadol (2 mg kg^{-1}) followed by atipamezole (Antisedan®, Pfizer Animal Health, Pennsylvania, USA) 0.05 mg kg^{-1} to antagonize xylazine 30 min after TZXT administration.

All drugs were drawn up individually and combined for administration as a single IM injection to the gluteal muscles. The washout period between experiments was 14 days.

Times from IM injection to lateral recumbency, sternal recumbency, standing and walking were recorded. Overall quality of sedation-anesthesia (sedation, analgesia, muscle relaxation, posture, and auditory response) was scored. For each study period, baseline physiologic parameters included heart rate (HR), respiratory rate (RR), noninvasive systolic, diastolic, and mean arterial blood pressure (SAP, DAP, and MAP), arterial oxygen hemoglobin saturation (SpO_2) and rectal temperature (RT) measured by noninvasive monitoring (Datex-OhmedaS/5TM, Datex-Ohmeda Division Instrumentarium Corp, Helsinki, Finland) before and after drug administration.

Scores for sedation-anesthesia were assigned at each time point according to the criteria described in Table 1. Responses to external stimuli were evaluated by measuring response to sound (3 hand claps). Muscle relaxant effects were evaluated by measuring jaw tone. Pinprick with a 22-gauge hypodermic needle was used to assess analgesia. The sequence of pinpricks was front limb along the radial-ulnar area followed by the perineal area near the base of the tail. Any gross purposeful movement of the limb or body in reaction to the pinprick was interpreted as lack of analgesia, and the analgesia scores were evaluated and recorded. Sedation-anesthesia evaluations occurred immediately after cardiorespiratory evaluation. All sedation-anesthesia evaluations occurred in the same order at each time point. The scoring criteria for sedation-anesthesia were established using a slight modification of previously published scoring methods (Lu *et al.*, 2011).

SPSS 13.0 was used for all statistical analyses. Induction, anesthesia, and standing and walking times were compared between groups by Student's *t*-test. Physiological parameters were analyzed by means of ANOVA for repeated measures to evaluate changes within each group and between 2 different treatments. The scores for sedation-anesthesia were compared using the Mann-Whitney test. A probability level of 5% ($P \leq 0.05$) was considered significant.

RESULTS

All 3 combinations induced sedation-anesthesia and lateral recumbency within 5 min after administration (Table 2). No vomiting, myoclonic twitching responses, or other adverse reactions were observed in the time between injection and recovery. There was no significant difference among the 3 treatment groups in onset of sedation or time from injection to lateral recumbency. The times from injection to first head lift, from injection to resumption of sternal recumbency, and time to resumption of standing and walking were significantly different between TZXT and TZXTA, but not between TZX and TZXTA.

Sedation scores for TZXT and TZX were significantly higher than the TZXTA treatment after atipamezole administration and for TZXT vs. TZX treatment at 60–80 min after administration of the combinations. Degree of response to sound was significantly higher at 5 min with TZXT and TZXTA treatment, while the scores were significantly lower at 60–80 min after TZX administration compared with TZXT treatment. Muscle relaxation and posture scores were significantly decreased after atipamezole injection and significantly lower at 60–80 min after TZX treatment compared with TZXT treatment. Response to pinpricks provided satisfactory indication of analgesia during the post-injection period. Analgesia scores after TZXT treatment and TZXTA treatment were higher than TZX treatment at 5 min, and posture scores were significantly decreased after atipamezole injection. Analgesia scores at 60–80 min after TZXT treatment were significantly higher than after TZX treatment (Table 3).

RT decreased over time after administration of the drug combinations in all treatments throughout the study (Table 4).

HR increased significantly at 10 min after administration of each combination. The TZX treatment had the lowest HR at 45 min after drug administration and the highest value at 70 min. HR decreased from 10 min until the 60 min, and had the highest HR at the end of the monitoring period in the TZXT group. Atipamezole

Table 1: Scoring criteria for posture, response to sound, response to contact, jaw tone and analgesia

Criteria	Score	Observation
Sedation		
	0	Normal
	1	Mild sedation (recumbent, head down, strong palpebral reflex, normal eye position)
	2	Moderate sedation (recumbent, head down, moderate palpebral reflex, partial ventromedial eye rotation)
	3	Profound sedation (recumbent, head down, palpebral reflex absence, complete ventromedial eye rotation)
Posture		
	0	Normal
	1	Sedated but able to stand
	2	Sternal recumbency
	3	Lateral recumbency with apparent spontaneous movement (head and/or limb)
	4	Lateral recumbency with subtle spontaneous movement (twitching and/or blinking)
	5	Lateral recumbency without spontaneous movement
Response to sound (response to noise created by a handclap close to the ears)		
	0	Normal response
	1	Mild decrease in response (eye movement with body movement)
	2	Moderate decrease in response (eye movement without body movement)
	3	Profound decrease in response (no movement)
Muscle relaxation		
	0	Normal jaw and leg tone
	1	Mild relaxation of jaw and leg tone
	2	Moderate relaxation and leg tone
	3	Profound relaxation of jaw and leg tone
Analgesia		
	0	Normal (productive flight response)
	1	Mild (exaggerated movements of limbs and trying to get up)
	2	Moderate (slight movements of the limbs and trying to get up)
	3	Profound (lack of response)

Table 2: Sedation anesthesia variables after intramuscular injection of Tiletamine-zolazepam/xylazine, Tiletamine-zolazepam/xylazine/tramadol, or Tiletamine-zolazepam/xylazine/tramadol/atipamezole in 8 dogs

Variable	Treatment		
	TZX	TZXT	TZXTA
Time from injection to onset of sedation (min)	2.33±0.45	2.05±0.37	2.07± 0.33
Time from injection to sternal recumbency (min)	3.43±0.28	3.14±0.36	3.20±0.29
Time from injection to lateral recumbency (min)	4.45±0.53	4.04±0.42	3.92±0.39
Time from injection to first head life (min)	44.53±5.75^{b}	77.78±6.74^{a}	33.21±5.63^{b}
Time from injection to resumption of sternal recumbency (min)	59.42±5.32^{b}	89.76±8.25^{a}	47.78±4.69^{b}
Time from injection to standing and walking (min)	78.47±8.55^{ab}	98.33±7.54^{a}	58.26±6.28^{b}

Different superscripts (a, b) within a row indicate a significant difference between treatment groups (P≤0.05).

Table 3: Mean (±SD) values for sedation, posture, response to sound, muscle relaxation, and analgesia in dogs anaesthetized with Tiletamine-zolazepam/xylazine, Tiletamine-zolazepam/xylazine/tramadol, or Tiletamine-zolazepam/xylazine/tramadol/atipamezole

Effect	Treatment	Time (Min)							
		0	5	10	30	45	60	70	80
Sedation	TZX	0	1.1±0.1	2.6±0.2	3.0	2.9±0.1^{a}	2.1±0.3^{b}	1.2±0.2^{b}	0.2±0.1^{b}
	TZXT	0	1.2±0.1	2.8±0.1	3.0	3.0^{a}	3.0^{a}	3.0^{a}	2.7±0.2^{a}
	TZXTA	0	1.2±0.1	2.7±0.2	3.0	1.2±2^{b}	0.2±0.1^{c}	0	0
Posture	TZX	0	3.3±0.1	4.7±0.3	5.0	4.8±0.1^{a}	2.7±0.2^{b}	1.8±0.2^{b}	0.5±0.1^{b}
	TZXT	0	3.5±0.2	4.8±0.2	5.0	5.0^{a}	5.0^{a}	5.0^{a}	3.8±0.3^{a}
	TZXTA	0	3.6±0.2	4.7±0.3	5.0	2.7±0.2^{b}	0.2±0.1^{c}	0	0
Response to sound	TZX	0	1.3±0.2^{b}	2.8±0.1	3.0	2.8±0.1^{a}	2.0±0.2^{b}	1.3±0.2^{b}	0.2±0.1^{b}
	TZXT	0	1.7±0.1^{a}	2.7±0.2	3.0	3.0^{a}	3.0^{a}	3.0^{a}	2.7±0.1^{a}
	TZXTA	0	1.8±0.1^{a}	2.8±0.1	3.0	1.1±0.2^{b}	0.4±0.2^{c}	0	0
Muscle relaxation	TZX	0	1.3±0.1	2.7±0.2	3.0	2.6±0.2^{b}	2.1±0.1^{b}	1.3±0.1^{b}	0.3±0.1^{b}
	TZXT	0	1.2±0.1	2.8±0.1	3.0	3.0^{a}	3.0^{a}	3.0^{a}	2.6±0.2^{a}
	TZXTA	0	1.3±0.1	2.8±0.1	3.0	1.0±0.1^{c}	0.3±0.1^{c}	0	0
Analgesia	TZX	0	1.8±0.2^{b}	2.8±0.1	3.0	2.7±0.2^{a}	1.8±0.2^{b}	1.4±0.1^{b}	0.3±0.1^{b}
	TZXT	0	2.2±0.2^{a}	2.6±0.1	3.0	3.0^{a}	3.0^{a}	3.0^{a}	2.6±0.2^{a}
	TZXTA	0	2.2±0.1^{a}	2.7±0.1	3.0	1.3±0.2^{b}	0.2±0.1^{c}	0	0

Different superscripts (a, b, c) within each effect are significantly different (P≤0.05).

administration at 30 min in the TZXTA treatment significantly increased HR at 45 min, and dogs in the TZXTA treatment groups showed higher HR than after other treatments at 45-60 min (Table 4). There were no episodes of severe rate disturbance after any treatment.

RR increased significantly at 10 min after TZX administration, decreased to the lowest values at 45 min, increased again from 60-70 min, and then decreased by 80 min. RR after TZXT treatment increased significantly at 10 min, then decreased 60 min, and reached the highest value at the end of the monitoring period. RR in TZXTA treatment tended to be significantly higher than baseline at 10 min after TZXT injection, and increased significantly at 15 min after atipamezole administration. Dogs with TZXTA treatment had higher RR than with other treatments from 40–60 min after injection of TZXT. SPO_2 changes had the same tendency as RR, and there were no significant changes within each treatment. The dogs had higher SPO_2 after TZXTA treatment than in other treatments at 45 min after TZXT injection (Table 4).

Table 4: Mean (±SD) values for physiological parameters evaluated in dogs anaesthetized with Tiletamine-zolazepam/xylazine, Tiletamine-zolazepam/xylazine/tramadol, or Tiletamine-zolazepam/xylazine/tramadol/atipamezole

	Time (min)	0	5	10	30	45	60	70	80
RT (°C)	TZX	39.1±0.2	39.0±0.2	38.7±0.1*	38.2±0.1*	37.7±0.2*	37.2±0.2*	37.1±0.1*	36.9±0.2*
	TZXT	38.9±0.3	38.8±0.2	38.5±0.1*	38.0±0.1*	37.5±0.1*	37.2±0.1*	37.0±0.3*	36.8±0.2*
	TZXTA	38.9±0.2	38.7±0.2	38.5±0.2*	38.0±0.1*	37.5±0.2*	37.1±0.1*	37.0±0.2*	36.8±0.1*
HR (beats minute^{-1})	TZX	115±12	121±13	138±16*	108±10	93±7*^{a}	109±10^{a}	141±17*^{b}	133±11
	TZXT	117±15	123±15	140±14*	106±11	92±6*^{a}	90±8*^{a}	95±10*^{a}	142±17*
	TZXTA	116±11	125±12	141±17*	105±15	152±17*^{b}	128±11^{b}	123±12^{b}	120±14
RR (breaths minute^{-1})	TZX	17±6	22±7	27±5*	18±6	13±2^{a}	18±4^{a}	28±4*^{b}	23±5^{ab}
	TZXT	17±7	23±6	28±7*	18±5	14±3^{a}	11±2^{a}	15±3^{a}	27±6*^{b}
	TZXTA	18±6	25±6	28±7*	16±7	37±6*^{b}	26±5^{b}	17±3^{a}	15±2^{a}
SpO_2 (%)	TZX	98±2	98±1	99±1	96±2	95±1^{a}	97±1^{b}	98±2	96±2^{a}
	TZXT	97±2	98±1	99±1	97±3	95±2^{a}	94±1^{a}	96±3	99±1^{b}
	TZXTA	97±3	98±2	98±2	96±1	99±1^{b}	97±2^{b}	96±2	95±1^{a}
SAP (mmHg)	TZX	135±14	145±13	163±18*	138±12	129±13^{a}	147±14^{b}	166±18*^{b}	150±15
	TZXT	130±16	149±17	162±19*	139±16	127±12^{a}	119±12^{a}	128±17^{a}	141±14
	TZXTA	130±17	152±18	166±15*	140±15	165±14*^{b}	143±16^{b}	130±15^{a}	126±14
DAP (mmHg)	TZX	98±11	103±12	117±11*	82±9	73±8*^{a}	96±10^{b}	122±8*^{b}	113±14
	TZXT	95±14	98±11	116±17	81±11	74±9^{a}	70±9^{a}	79±10^{a}	117±18
	TZXTA	95±13	107±15	120±15*	80±9	125±11*^{b}	95±11^{b}	93±9^{a}	92±11
MAP (mmHg)	TZX	115±11	121±10	135±12*	99±10	94±8*^{a}	112±12^{b}	138±13*^{b}	123±15
	TZXT	109±12	120±13	135±15*	102±12	93±11^{a}	86±9*^{a}	96±10^{a}	127±11
	TZXTA	110±14	125±11	138±11*	100±14	135±13*^{b}	113±12^{b}	104±14^{a}	106±10

*significantly ($P<0.05$) different from values at 0 minutes within each group; Different superscripts (a, b) within each time in same physiological parameters are significantly different ($P\leq0.05$).

In all groups, SAP, DAP and MAP increased significantly from baseline at 10 min. SAP, DAP and MAP decreased from 10 to 45 min, and increased significantly at 70 min in the TZX group. The TZXA treatment had the lowest blood pressures at 60 min after drug administration and the highest value at the end of the monitoring period. SAP, DAP and MAP reached the highest value at 45 min in TZXTA treatment. Dogs had higher blood pressures with the TZXTA treatment than the other treatments at 45 min after injection of TZXT (Table 4).

DISCUSSION

This study demonstrated that both TZX and TZXT are effective injectable induction and sedation combinations. Dogs that received IM administration of either TZX or TZXT had onset of sedation and lateral recumbency within 4-5 min after drug administration. The duration of sedation was longer and tolerance to pinprick higher with TZXT treatment, possibly indicating the combined effect of the analgesic properties of tramadol. In a clinical situation, the longer duration of sedation-anesthesia with TZXT treatment is adequate for minor surgical procedures.

When all treatments were compared, there were similar sedation, muscle relaxation, and posture scores at 5 min. Degrees of sedation, analgesia, and muscle relaxation, as well as effects on posture and response to sound, was greater in TZXTA and TZXT groups until 30 min as compared to TZX group. This can be attributed to the effect of tramadol, which extends sedation-anesthesia time when compared with TZX alone. The influence of tramadol may also explain the longer times to standing and walking observed with TZXT group. Atipamezole is known to be effective for reversal of sedation and analgesia caused by xylazine in dogs (Talukder *et al.*, 2009). The dose of atipamezole selected for this study were considered equivalent in terms of antagonism of xylazine for the antidotal procedure shortening the recovery period in dogs anesthesia with TZXT, and adverse effects such as rigidity of limbs, muscle tremors, and excitement were not observed. The atipamezole-to-xylazine ratio of 1:10 has been successfully used in pigs previously (Lu *et al.*, 2011), and it did not cause any undesirable effects or resedation in this study.

We hypothesized that the antagonism of xylazine by atipamezole in the TZXTA group would provide good recovery quality with shortened recovery time. We expected the atipamezole antagonism of xylazine to be so clearly demonstrated that a sham injection of saline in the TZXT group at 30 min was planned. It was not a surprise that the administration of atipamezole significantly shortened recovery time, and the treated dogs showed more signs of arousal between 30 and 50 min, including lower total score, increased head lifting, and more frequent attempts to assume sternal recumbency. Based on our findings, we recommend that if a short (<30 min), minimally painful procedure is performed on a dog anesthetized with a TZXT combination, atipamezole can be used to avoid a long duration of profound central nervous system depression.

The RT decreased immediately after injection in all 3 treatments in this study, possibly because of the loss of thermoregulatory control following administration of alpha-2 adrenoceptor agonists (Lu *et al.*, 2013). The decrease in temperature may also be due to generalized sedation, decrease in metabolic rate, muscle relaxation, and central nervous system depression (Lu *et al.*, 2013). Our data indicated that the fall in temperature was not halted or antagonized by atipamezole.

The HR changed after administration of all drug combinations, and no anticholinergic agent was used, but there was no significant difference among the 3 treatment groups until 30 min, indicating that tramadol produced less pronounced cardiovascular depression and suggesting that the positive chronotropic effects of tiletamine/zolazepam probably temporarily and partially counterbalance the bradycardic effect of xylazine (Kim *et al.*, 2007). Atipamezole has been shown to antagonize cardiovascular depression effect treated with medetomidine (Rioja *et al.*, 2008), and in the current

study, HR in the TZXTA treatment groups increased significantly after atipamezole injection. Increased HR after atipamezole injection may be caused by a central stimulant effect and by a peripheral effect on the vascular bed, which can induce transient vasodilative hypotension and reflex increase in HR (Pertovaara *et al.*, 2005). Tachycardia after administration of atipamezole in dogs can be an undesirable side effect (Ko *et al.*, 2007), but in our study the elevations in HR after atipamezole administration were not severe.

Similar RR were observed in all 3 treatment groups until 35 min after drug administration and none of the 3 combinations had a significant effect on SpO_2. This may be partially due to the tramadol, because a major advantage of tramadol compared with other opioids is its lack of cardiopulmonary depressant effects (Ajadi *et al.*, 2009). Atipamezole has been shown to antagonize the respiratory inhibition induced by xylazine and medetomidine (Rioja *et al.*, 2008), and in the present study, RR increased after injection of the antagonist. Blood gas analysis and end-tidal carbon dioxide would be needed to more precisely evaluate respiratory function following drug administration.

Blood pressure was well maintained in all 3 treatment groups in the current study. There were no significant differences in blood pressure in any treatment group until 35 min after drug administration, indicating that the addition of tramadol had little effect on blood pressure. Blood pressure is known to show peak increase for about 5-10 min and then to fall below baseline values after xylazine administration in dogs (Ilbäck and Stålhandske, 2003), which can partially explain the changes in blood pressure seen in this study. The addition of atipamezole significantly increased blood pressure in TZXT-treated dogs compared with TZXA treatment at 40-50 min.

Conclusion: A single IM injection of TZX or TZXT induced good anesthesia in healthy dogs. The duration of anesthesia of these combinations was approximately 70–90 min, with durations of adequate surgical analgesia of 45 min for TZX and 75 min for TZXT. Cardiorespiratory responses were characterized by well-maintained blood pressure and respiratory rates, and no adverse effects were observed. Antagonism of xylazine by atipamezole was effective in shortening the anesthesia time and allowed dogs to become alert somewhat earlier.

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