

# Comparison of Anesthetic and Cardiorespiratory Effects of Tiletamine–Zolazepam–Butorphanol and Tiletamine–Zolazepam–Butorphanol–Medetomidine in Dogs\*

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## CLINICAL RELEVANCE

This study compared anesthetic and cardiorespiratory effects of tiletamine–zolazepam–butorphanol (TT), tiletamine–zolazepam–butorphanol–medetomidine (TTD), and tiletamine–zolazepam–butorphanol–medetomidine with atipamezole reversal 1 hour after TTD administration in dogs. All dogs received glycopyrrolate. All drug combinations effectively induced anesthesia within 5 minutes after IM injection. Duration of analgesia was 40 to 60 minutes. Recovery was smooth, but the overall quality of recovery was poorer in the TT group. Hypoxia occurred with some dogs in the TTD group at 5 minutes. TTD provided better analgesia with longer duration and better recovery quality compared with TT. Reversal of TTD with atipamezole was not effective in shortening recovery time.

## INTRODUCTION

The tiletamine–zolazepam–ketamine–xylazine (TKX) combination was initially introduced more than a decade ago for use in cats undergoing onychectomy and castration.<sup>1</sup> It has since gained popularity, especially in high-volume animal shelters and for elective procedures in cats.<sup>2,3</sup> The TKX combination was

mainly designed for use in cats and was not completely suitable for use in dogs because the ketamine purposefully changed the 1:1 proprietary ratio of tiletamine:zolazepam to reduce the prolonged recovery induced by higher doses of zolazepam in cats.<sup>1</sup> Ketamine tends to induce muscle rigidity in dogs, resulting in prolonged, rough recoveries when the actions of tiletamine

\*This study was funded by a research grant from Fort Dodge Animal Health, Overland Park, Kansas.

and ketamine become evident in the TKX combination. Another drawback of the TKX combination is the lack of an opioid to produce an analgesic effect once xylazine is reversed.

With the advancement of  $\alpha_2$  agonist development, xylazine is less commonly used in small animals today and has been largely replaced by medetomidine. When used in combinations with butorphanol or ketamine, medetomidine induces reliable sedation and analgesia in dogs.<sup>4-6</sup> It is reasonable to assume that combining tiletamine–zolazepam with medetomidine and butorphanol would result in a suitable injectable anesthetic protocol with rapid onset of anesthesia and good analgesia in dogs. Tiletamine–zolazepam with butorphanol is an alternative in-

administration of TTD would shorten recovery time without affecting recovery quality.

## ■ MATERIALS AND METHODS

This study was approved by the Oklahoma State University Animal Care and Use Committee. Seven dogs (five females and two males; mean body weight:  $20.2 \pm 3.0$  kg) were used in the crossover study, with each dog receiving three IM drug combinations administered in random order:

- **TT:** Tiletamine–zolazepam (Telazol, Fort Dodge Animal Health; 5 mg/kg) and butorphanol (Torbugesic, Fort Dodge Animal Health; 0.2 mg/kg)

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### *All three combinations rapidly induced sedation–anesthesia and lateral recumbency.*

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jectable combination in dogs. To compare and contrast these two combinations, this study was designed to assess the anesthetic and analgesic effects following drug administration.

The objectives of this study were to evaluate and compare the anesthetic and cardiorespiratory effects of tiletamine–zolazepam–butorphanol (TT [Telazol–Torbugesic]) and tiletamine–zolazepam–butorphanol–medetomidine (TTD [Telazol–Torbugesic–Domitor]). It was hypothesized that TTD would have a longer duration of anesthesia and better-quality analgesic effects than TT and that using atipamezole to reverse medetomidine in the TTD combination would allow for the assessment of recovery time compared with TTD. Atipamezole was given 60 minutes after TTD administration to allow adequate time for metabolism of tiletamine, thereby avoiding residual tiletamine effects during recovery. It was hypothesized that the use of atipamezole 1 hour after

- **TTD:** Tiletamine–zolazepam (3 mg/kg), butorphanol (0.15 mg/kg), and medetomidine (Domitor, Pfizer Animal Health; 15  $\mu$ g/kg)
- **TTDA:** Tiletamine–zolazepam (3 mg/kg), butorphanol (0.15 mg/kg), medetomidine (15  $\mu$ g/kg) followed by atipamezole (Antisedan, Pfizer Animal Health; 75  $\mu$ g/kg IV) to reverse medetomidine 1 hour after TTD administration

Lower doses of tiletamine–zolazepam and butorphanol were used in the TTD and TTDA groups because of the anticipated augmentation of central nervous system depression and analgesia by medetomidine. Glycopyrrolate (0.01 mg/kg IM) was administered with each combination. All drugs were drawn up separately and administered together as a single IM injection. All dogs breathed room air throughout each study period. Body temperatures were maintained between 99°F and 101°F with a

water-circulating heating blanket and towels. The washout period between treatments was at least 1 week and, in some cases, up to 2 weeks.

Time from IM injection to lateral recumbency, endotracheal intubation, recovery, sternal recumbency, and standing and walking (not just standing and then falling back into sternal recumbency) were recorded. Overall quality of sedation–anesthesia was scored, as was quality of recovery (Table 1). Investigators were not blinded to treatment.

For each study period, a 4.45-cm, 20-gauge catheter (Angio-cath, Becton-Dickinson Vascular Access, Sandy, UT) was placed in a dorsal pedal artery before drug administration to allow measurement of arterial blood pressure and collection of arterial blood samples for analysis of blood gas partial pressures. The catheter was attached to a blood pressure transducer (Passport Datascope, Passport Corporation, Paramus, NJ) that was calibrated before each study period by use of a mercury manometer (Model 300 Baumometer, W. A. Baum Co., NY).

Baseline heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial pressure (MAP), rectal temperature, and blood gas partial pressures were measured and a lead II electrocardiographic rhythm was monitored immediately before and after drug administration. Arterial blood pH, partial pressure of oxygen ( $\text{PaO}_2$ ), partial pressure of carbon dioxide ( $\text{PaCO}_2$ ), and lactate concentration were

measured by use of a blood gas analyzer (i-STAT blood gas analyzer, Heska, Fort Collins, CO) and corrected for rectal temperature.

After baseline data (time 0) were collected, dogs were immediately given the drug combination IM. Arterial blood pressure, HR, and RR were measured at 5, 10, 20, 30, 40, 50, and 60 minutes after drug administration and, in the TTDA group, again at 65 minutes after TTD administration (i.e., 5 minutes after atipamezole IV injection). Saturation of hemoglobin with oxygen ( $\text{SpO}_2$ ) was monitored with

**TABLE 1. Central Nervous System Depression and Recovery Scoring System Used to Evaluate Dogs**

<i>Score</i>	<i>Description</i>
<b>Sedation–Anesthesia</b>	
1	Reduced activity only
2	Mild sedation: mildly aware of the surrounding environment
3	Moderate sedation: eyes droopy, head down, inactive, sternal recumbency, unable to be intubated
4	Profound sedation–anesthesia: no movement, rapid assumption of lateral recumbency with great muscle relaxation and easy intubation
<b>Recovery</b>	
1	Prolonged struggling, unable to stand without assistance, hyperkinesis in response to manual assistance, increased rectal temperature associated with increased struggling resulting in increased metabolism
2	Some struggling, repeated attempts to stand, assistance required to stand, significant instability and inability to maintain balance while walking, some signs of drug hangover
3	Some struggling, some assistance required to stand, ability to maintain balance once standing, minimal signs of drug hangover
4	Resumption of sternal recumbency with little or minimal struggling, ability to stand and walk with minimal effort, no signs of drug hangover

**TABLE 2. Sedation–Anesthesia Variables after IM Administration of Tiletamine–Zolazepam–Butorphanol (TT), Tiletamine–Zolazepam–Butorphanol–Medetomidine (TTD), and Tiletamine–Zolazepam–Butorphanol–Medetomidine Reversed with Atipamezole (TTDA) in Seven Dogs<sup>\*†</sup>**

Variable	Treatment		
	TT (n = 7)	TTD (n = 7)	TTDA (n = 7)
Time from injection to onset of sedation (min)	2.28 ± 0.28	2.14 ± 0.34	2.42 ± 0.36
Time from injection to sternal recumbency (min)	3.42 ± 0.29	3.14 ± 0.34	3.28 ± 0.42
Time from injection to lateral recumbency (min)	4.57 ± 0.57	3.85 ± 0.40	4.14 ± 0.45
Time from injection to orotracheal intubation (min)	7.00 ± 0.57	5.14 ± 0.59	5.85 ± 0.50
Duration of intubation (min)	40.71 ± 3.98 <sup>a</sup>	57.0 ± 4.30 <sup>b</sup>	59.85 ± 6.00 <sup>b</sup>
Duration of lateral recumbency (min)	53.14 ± 6.91 <sup>b</sup>	82.85 ± 8.58 <sup>a</sup>	87.85 ± 9.51 <sup>a</sup>
Time from injection to first head lift (min)	51.00 ± 4.83	61.14 ± 7.86	66.00 ± 4.35
Time from injection to resumption of sternal recumbency (min)	53.14 ± 6.91 <sup>b</sup>	82.85 ± 8.58 <sup>a</sup>	87.85 ± 9.51 <sup>a</sup>
Time from injection to standing and walking (min)	81.26 ± 8.85	88.42 ± 8.45	102.14 ± 9.43
Overall quality of sedation <sup>‡</sup>	3.85 ± 0.14	4.00 ± 0.00	4.00 ± 0.00
Overall quality of recovery <sup>‡</sup>	2.43 ± 0.29 <sup>b</sup>	3.50 ± 0.24 <sup>a</sup>	3.14 ± 0.26 <sup>a</sup>

<sup>\*</sup>Data presented as mean ± SEM. A row without superscripts indicates no significant difference between treatment groups.

<sup>†</sup>See Table 1 for scoring system to evaluate sedation and recovery.

<sup>a,b</sup>Different superscripts within a row indicate a significant difference between treatment groups ( $P \leq .05$ ).

a lingual probe (Nellcor N-20PA, Nellcor-Puritan, Pleasanton, CA) from injection until recovery. Blood gas variables were measured at baseline and 5, 10, 20, 40, and 50 minutes after drug administration.

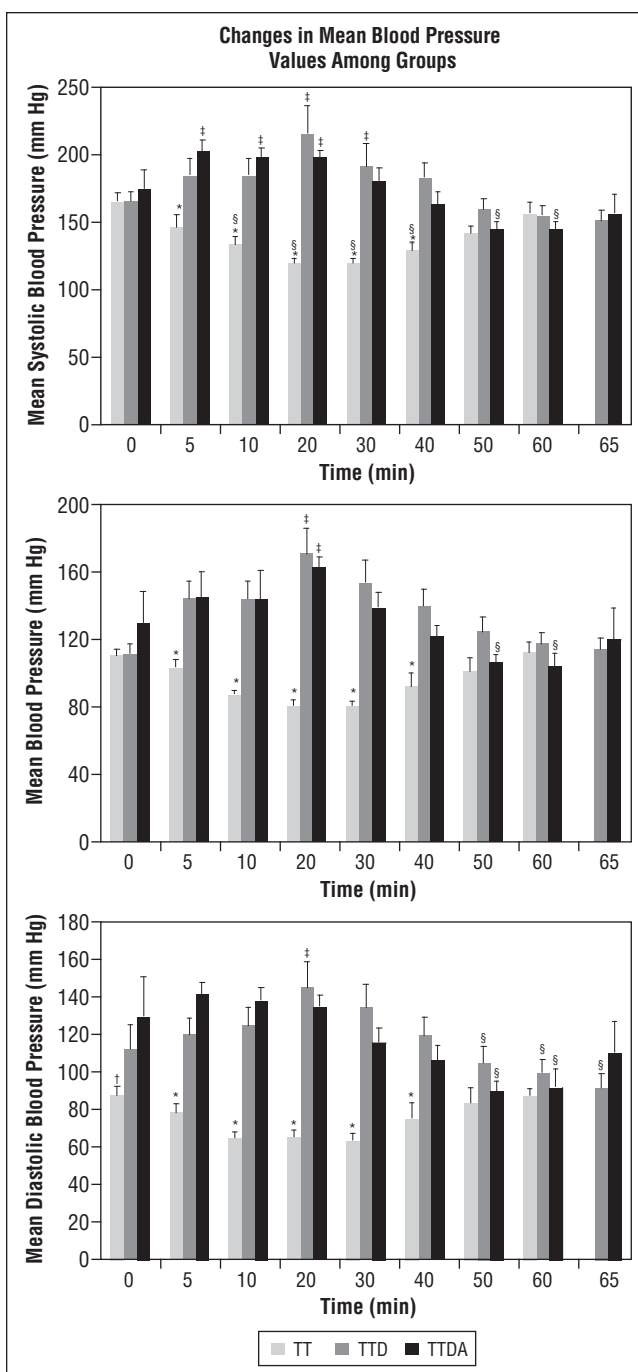
Three methods were used to assess analgesia. The first method utilized an algometer. The use of an algometer for determination of pain thresholds for pressure application in soft tissue, muscles, and joints has been demonstrated in humans<sup>7</sup> and horses.<sup>8</sup> The algometer used in this study (Somedic Algometer type II, Somedic Production AB, Stockholm, Sweden) was equipped with a squeeze handle; when squeezed, two nontraumatizing sensors exert a noxious pressure, expressed in kilopascals (kPa; device range: 0 to 2,000 kPa), on the tissue of

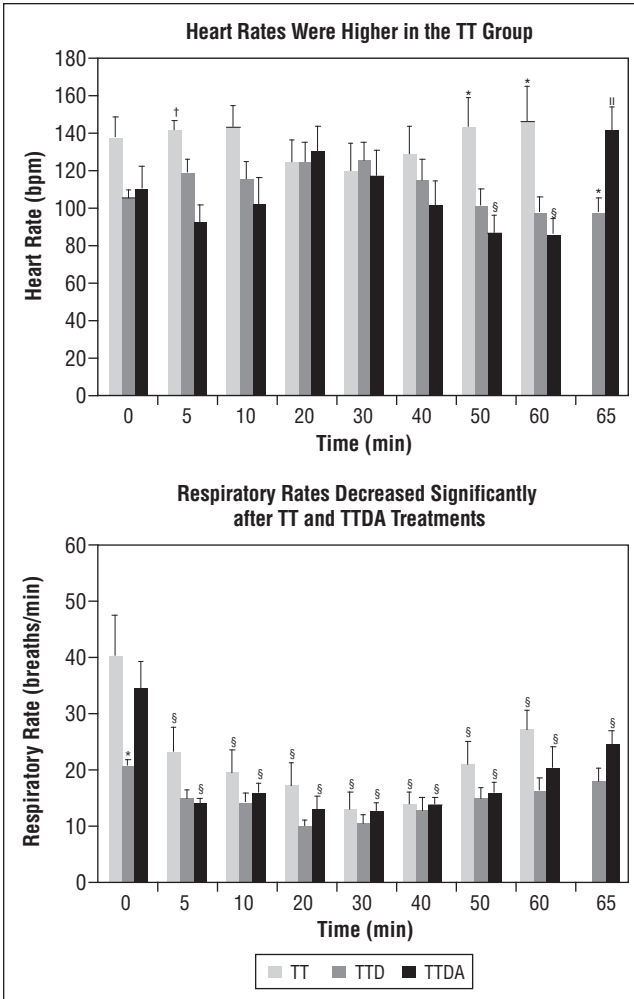
the patient being evaluated. Once the dog exhibited a sign of pain, including withdrawal the limb, head lift, or other purposeful movements related to this noxious stimulus, the algometer was released and the pressure recorded. The algometer was applied on the dog's front toe digit and mid-portion of the tail. Before each study, the algometer pressure was calibrated against a weight to ensure its accuracy. The second method used a nerve stimulator (Peripheral Nerve Stimulator Model 100A, Anesthesia Associates, San Marcos, CA) attached to the skin of the hindlimb distal to the knee with two alligator clips for electrical stimulation. The nerve stimulator was set at tetanus mode with 100 pulses/second and four intensity scales, with one being the lowest setting

and four being the strongest. At each time point, the tetanus stimulation was turned on for 1 second. The level at which there was no response (gross purposeful movements, including limb withdrawal, tail twitching, moving of the neck) was determined and recorded. If a test was positive, then the strength was reduced by one level and the animal tested again; if a test was negative, the strength was increased by one level until a positive response or a maximal level was achieved.

A needle prick with a 22-gauge hypodermic needle was the third method to assess analgesia. The needle prick analgesic test was a “yes” or “no” response. When there was a positive response such as limb withdrawal, skin twitching, or any other purposeful movements in reaction to the needle pricking, the response was recorded as “no” analgesia. When there was no response, the animal was considered “yes” for analgesia until the next stimulus was applied. This method has been previously used in several species for assessing anal-

**Figure 1.** Blood pressure following IM administration of tiletamine-zolazepam-butorphanol (TT), tiletamine-zolazepam-butorphanol-medetomidine (TTD), and tiletamine-zolazepam-butorphanol-medetomidine reversed with atipamezole (TTDA) in seven dogs. All data are presented as mean  $\pm$  SEM. \*Significantly different from other treatments. †Significantly different from TTDA. ‡Significantly higher than baseline within treatment. §Significantly lower than baseline within treatment.





**Figure 2.** Cardiorespiratory variables following IM administration of tiletamine-zolazepam-butorphanol (TT), tiletamine-zolazepam-butorphanol-medetomidine (TTD), and tiletamine-zolazepam-butorphanol-medetomidine reversed with atipamezole (TTDA) in seven dogs. All data are presented as mean  $\pm$  SEM. \*Significantly different from other treatments. †Significantly different from TTDA. §Significantly lower than baseline within treatment. ||Significantly different from the previous time point (60 minutes).

or body portion in reaction to the needle pricking was interpreted as lack of analgesia, and the duration of analgesia was recorded.

Analgesia evaluations occurred at 0, 5, 10, 20, 30, 40, 50, 60, and 65 minutes after drug administration; the time 0 evaluation was done using only the algometer, and the evaluation at 65 minutes was done using only the nerve stimulator. All pain assessment evaluations occurred in the same order (algometer, nerve stimulator, and needle prick) at each time point in each dog.

**Statistical Analysis**

PC SAS (SAS Institute, Cary, NC) was used for all statistical analyses. Analysis of variance (ANOVA) techniques (PROC MIXED in SAS, Version 9) were used to assess treatment difference in anesthesia, analgesia, and cardiorespiratory data. When multiple observations were made for the same subject, repeated measures models were utilized with an autoregressive period 1 covariance structure to account for within-subject correlations. Effects of treatments were presented as pairwise *t*-tests when a significant difference ( $P < .05$ ) was detected in the ANOVA. In the case of the repeated measures analyses, simple effects of treatments for given time intervals

were presented if the overall effect of treatment was significant using a SLICE option in an LSMEANS statement (PROC MIXED). All results are reported as mean  $\pm$  SEM.

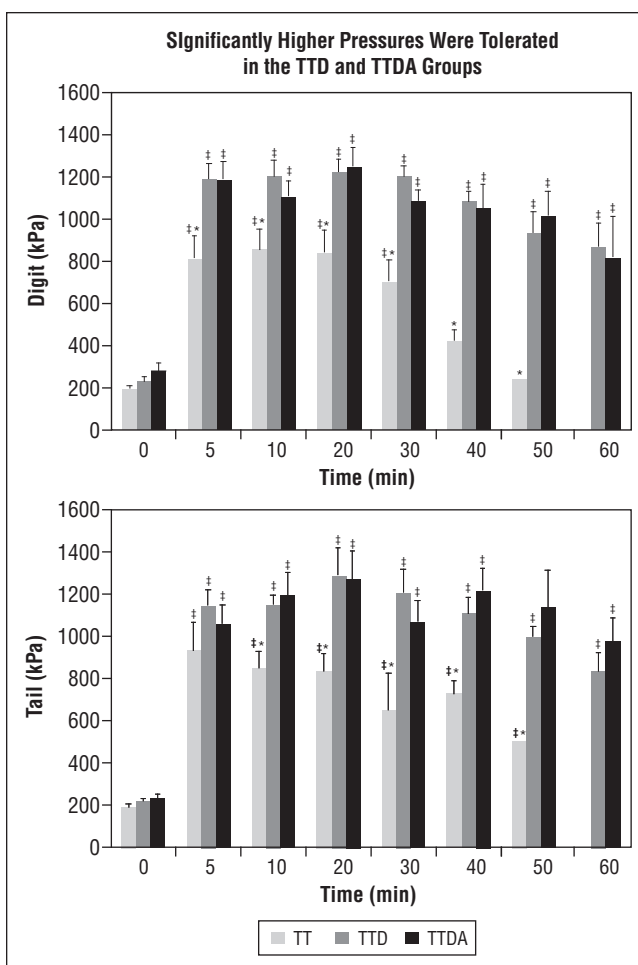
gesia.<sup>9-12</sup> The sequence of needle pricking was front limb near the radial-ulna area, ventral mid-line of the abdomen, and rear limb near the tibial area. Any gross purposeful moving of the limb

were presented if the overall effect of treatment was significant using a SLICE option in an LSMEANS statement (PROC MIXED). All results are reported as mean  $\pm$  SEM.

## RESULTS

All three combinations rapidly induced sedation–anesthesia and lateral recumbency within 5 minutes after IM administration (Table 2). All dogs were intubated with ease within 5 to 7 minutes. There was no significant difference among the three treatment groups in onset of sedation and time from injection to lateral recumbency and intubation. However, the duration of intubation, duration of lateral recumbency, and time from injection to sternal recumbency was significantly shorter with TT than with TTD or TTDA (Table 2). The quality of recovery was less with TT than with TTD or TTDA.

Mean blood pressure values are presented in Figure 1. Baseline SAP and MAP were not significantly different between treatment groups, but baseline DAP was lower in the TT treatment group than in the TTDA group. SAP in the TT-treated dogs was significantly lower than baseline from 10 to 40 minutes after drug administration. In contrast, SAP was significantly higher than baseline at 20 and 30 minutes after drug administration in the TTD group and at 5, 10, and 20 minutes in the TTDA group. There was no significant change in MAP or DAP from baseline in the TT-treated dogs. SAP, MAP, and DAP were significantly higher from 5 to 40 minutes in the TTD and TTDA groups than in the TT group. Other differences in blood pressures are also presented in Figure 1.



**Figure 3.** Analgesia evaluation via pressure algometer following IM administration of tiletamine–zolazepam–butorphanol (TT), tiletamine–zolazepam–butorphanol–medetomidine (TTD), and tiletamine–zolazepam–butorphanol–medetomidine reversed with atipamezole (TTDA) in seven dogs. All data are presented as mean  $\pm$  SEM. \*Significantly different from other treatments. †Significantly greater than baseline within treatment.

Cardiorespiratory variables are presented in Figure 2. Baseline HRs were not significantly different between treatment groups. The TT group had higher HRs 5 minutes after drug administration, and three dogs had an HR below 60 bpm during the first 5 minutes after

TTD or TTDA administration. At 50 and 60 minutes, HRs were higher in the TT group than in the TTD and TTDA groups. Besides bradycardia, no other types of arrhythmias were observed in any of the treated dogs.

Atipamezole administration at 60 minutes in the TTDA treatment group significantly increased HR from 86.5 ± 8.2 bpm to 142.5 ± 23.2 bpm at 65 minutes (Figure 2). This HR was also significantly higher than that in the TTD group (98.7 ± 7.0 bpm) at 65 minutes. Atipamezole administration did not result in significant changes in RR, SAP, MAP, DAP, or SpO<sub>2</sub> versus 60-minute values within the TTDA group or when compared with the TTD group at 65 minutes. Although the time from drug injection to walking was shorter with TTD (88.4 ± 8.4 minutes) than with TTDA (102.1 ± 9.4 minutes), this was not statistically significant. There was no statistically significant difference in time from drug administration to sternal recumbency or standing and walking between TTD and TTDA treatment groups.

Following drug administration, RRs decreased significantly from baseline in both TT and TTDA treatment groups at 5 minutes after drug administration and continued until the end of the experiment. RRs did not change significantly from the baseline the TTD group (Figure 2).

PaO<sub>2</sub> decreased significantly from baseline in all three treatment groups (Table 3). The lowest PaO<sub>2</sub> tensions were 55 and 58 mm Hg in

**TABLE 3. Blood Gas Variables after IM Administration of Tiletamine–Zolazepam–Butorphanol (TT), Tiletamine–Zolazepam–Butorphanol–Medetomidine (TTD), and Tiletamine–Zolazepam–Butorphanol–Medetomidine Reversed with Atipamezole (TTDA) in Seven Dogs\***

Variable	Treatment		
	TT (n = 7)	TTD (n = 7)	TTDA (n = 7)
<b>PaO<sub>2</sub> (mm Hg)</b>			
0 min	90.57 ± 2.16 <sup>a</sup>	86.43 ± 1.66 <sup>a</sup>	88.57 ± 1.19 <sup>a,b</sup>
5 min	67.28 ± 4.31 <sup>a,1,2</sup>	58.71 ± 6.51 <sup>c,2</sup>	72.71 ± 3.77 <sup>c,1</sup>
10 min	71.71 ± 3.85 <sup>c,d,1</sup>	67.00 ± 4.65 <sup>b,1</sup>	82.29 ± 2.20 <sup>b,2</sup>
20 min	75.71 ± 3.36 <sup>b,c,1</sup>	69.00 ± 4.32 <sup>b,1</sup>	87.43 ± 1.97 <sup>a,b,2</sup>
40 min	80.14 ± 3.28 <sup>b,1</sup>	80.00 ± 2.30 <sup>a,1</sup>	90.57 ± 1.90 <sup>a,2</sup>
50 min	90.43 ± 1.52 <sup>a</sup>	84.14 ± 2.15 <sup>a</sup>	93.43 ± 0.37 <sup>a</sup>
<b>PaCO<sub>2</sub> (mm Hg)</b>			
0 min	34.81 ± 1.42	38.03 ± 0.86	34.03 ± 2.07
5 min	39.07 ± 1.79	40.41 ± 0.89	36.57 ± 2.04
10 min	39.91 ± 1.48	40.81 ± 0.59	37.83 ± 2.23
20 min	41.23 ± 2.13	42.79 ± 1.61	36.29 ± 1.06
40 min	39.16 ± 1.71	41.51 ± 2.34	34.57 ± 0.97
50 min	38.87 ± 1.77	39.21 ± 2.00	34.37 ± 0.77
<b>HCO<sub>3</sub> (mEq/L)</b>			
0 min	22.53 ± 0.83	22.26 ± 0.36	21.94 ± 0.32
5 min	22.97 ± 0.63	22.69 ± 0.69	22.06 ± 0.45
10 min	23.51 ± 0.48	22.31 ± 0.35	22.33 ± 0.67
20 min	23.87 ± 0.93	23.03 ± 0.42	22.57 ± 0.59
40 min	23.89 ± 0.96	23.47 ± 0.61	23.60 ± 0.67
50 min	24.51 ± 0.87	23.60 ± 0.78	22.84 ± 0.49

\*Data presented as mean ± SEM. A row or column without superscripts indicates no significant difference between treatment groups.

<sup>a,b,c,d</sup>Different alphabetic superscripts within a column indicate a significant difference within treatment groups (P ≤ .05).

two dogs at 5 minutes after TTD treatment. None of the TT or TTDA dogs had PaO<sub>2</sub> tension below 60 mm Hg. All PaCO<sub>2</sub> values were within 35 to 45 mm Hg, and none of the dogs became apneic (Table 3). An apneustic breathing pattern was observed in some dogs after all three treatments. All arterial lactate concentrations were within the normal range (0.6 to 2.9 mmol/dl) and did not differ significantly over

Variable	Treatment		
	TT (n = 7)	TTD (n = 7)	TTDA (n = 7)
<b>pH</b>			
0 min	7.41 ± 0.01	7.36 ± 0.01	7.36 ± 0.02
5 min	7.38 ± 0.01	7.35 ± 0.01	7.35 ± 0.01
10 min	7.39 ± 0.01	7.35 ± 0.01	7.35 ± 0.01
20 min	7.36 ± 0.01	7.34 ± 0.01	7.34 ± 0.01
40 min	7.38 ± 0.01	7.35 ± 0.01	7.35 ± 0.01
50 min	7.39 ± 0.01	7.37 ± 0.01	7.36 ± 0.01
<b>SaO<sub>2</sub> (%)</b>			
0 min	97.00 ± 0.69	97.71 ± 0.36	97.29 ± 0.57
5 min	90.57 ± 2.35	84.71 ± 3.63	93.4 ± 3.32
10 min	93.14 ± 1.68	91.43 ± 1.27	96.43 ± 1.70
20 min	93.57 ± 1.21	90.43 ± 1.59	97.86 ± 0.83
40 min	93.57 ± 0.72	94.43 ± 1.02	98.43 ± 0.81
50 min	97.29 ± 0.64	95.43 ± 0.81	99.00 ± 0.53
<b>Lactate (mmol/dl)</b>			
0 min	1.43 ± 0.30 <sup>a</sup>	0.97 ± 0.15	1.04 ± 0.12
5 min	1.15 ± 0.19 <sup>b</sup>	0.98 ± 0.12	1.00 ± 0.14
10 min	1.13 ± 0.19 <sup>b</sup>	0.96 ± 0.09	0.95 ± 0.11
20 min	0.99 ± 0.18 <sup>b</sup>	0.96 ± 0.09	0.96 ± 0.14
40 min	0.73 ± 0.12 <sup>c</sup>	0.74 ± 0.07	0.75 ± 0.09
50 min	0.68 ± 0.09 <sup>c</sup>	0.66 ± 0.04	0.62 ± 0.06

<sup>1,2</sup>Mean values with different numerical superscripts indicate a significant difference between treatment groups.

HCO<sub>3</sub> = bicarbonate; PaCO<sub>2</sub> = partial pressure of arterial carbon dioxide; PaO<sub>2</sub> = partial pressure of arterial oxygen; SaO<sub>2</sub> = arterial oxygen hemoglobin saturation.

time between treatment groups (Table 3); however, arterial lactate decreased significantly within the TT-treated dogs between 5 and 50 minutes.

Analgesia as assessed by algometer (Figure 3) showed a significant increase from baseline in pressure tolerance on both digit and tail locations by 5 minutes after all three treatments. Significantly higher pressures were tolerated in

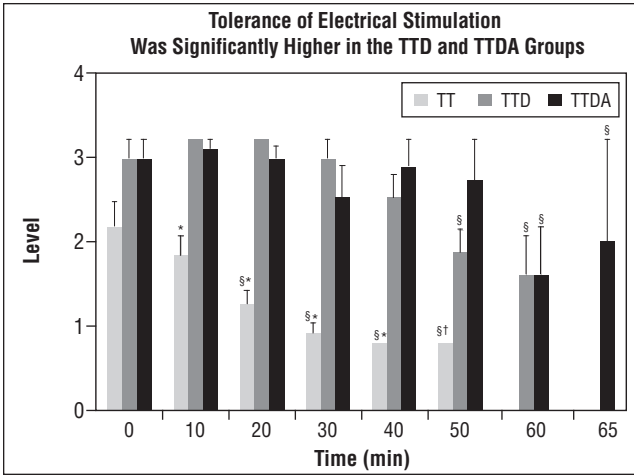
the TTD and TTDA groups than in the TT group from 10 to 50 minutes (Figure 3). Both TTD and TTDA also induced a significantly longer duration of analgesia (60 minutes) than did TT (40 minutes). By 60 minutes after drug administration, most of the dogs treated with TT were already recovering and the analgesic test was discontinued.

The results of analgesia assessed with the nerve stimulator were similar to those of the algometer assessments. The tolerance of electrical stimulation was significantly higher between 10 and 40 minutes in the TTD and TTDA treatment groups than in the TT group (Figure 4).

The duration of lack of response to needle pricking was significantly shorter with TT (approximately 30 minutes) than with TTD (50 minutes) and TTDA (45 minutes) in all three regions tested (Figure 5).

## DISCUSSION

This study demonstrated that both TT and TTD were effective injectable induction and anesthetic combinations. Dogs that received IM administration of either TT or TTD assumed lateral recumbency and allowed orotracheal intubation within 5 to 8 minutes after drug administration. The duration of tolerance of endotracheal intubation was longer than the duration of analgesia in all three treatment groups, possibly indicating a combined effect from the antitussive properties of butorphanol and the anesthetic-hypnotic properties of both tiletamine-zolazepam and



**Figure 4.** Analgesia evaluation via nerve stimulator following IM administration of tiletamine–zolazepam–butorphanol (TT), tiletamine–zolazepam–butorphanol–medetomidine (TTD), and tiletamine–zolazepam–butorphanol–medetomidine reversed with atipamezole (TTDA) in seven dogs. All data are presented as mean ± SEM. \*Significantly different from other treatments. †Significantly different from TTDA. §Significantly lower than baseline within treatment.

medetomidine. In a clinical situation, this long duration of endotracheal tube tolerance allows for protection of the airway and an easy switch to inhalant anesthesia even if the analgesic–anesthetic effect of the injectable drugs is no longer adequate for a surgical procedure.

In this study, it was hypothesized that the reversal of medetomidine by atipamezole in the TTDA group would shorten recovery time without affecting recovery quality. The reversal of medetomidine was expected to be so clearly demonstrated that a sham injection of saline in the TTD group at 60 minutes was believed to be unnecessary. It was a surprise that the administration of atipamezole did not significantly shorten recovery time. The duration from drug administration to sternal recumbency and walking was not significantly different between the TTD and TTDA groups. In fact, recovery from sternal recumbency to walking

was a bit longer in the TTDA group (Table 2). Atipamezole was given 60 minutes after TTD administration to avoid unopposed tiletamine effects (such as head bobbing, weaving, and increased muscle tone). Explanations for the lack of reversal effect after atipamezole administration include the possible near-complete metabolism of medetomidine by 60 minutes after administration of TTDA, which would render the reversal actions of atipamezole useless, or even more likely, the effect of other drugs within the combination continued to exert anesthetic or sedative effects. This was supported by the observation that dogs demonstrated dissociative signs and made more attempts to stand and walk after atipamezole reversal. The overall

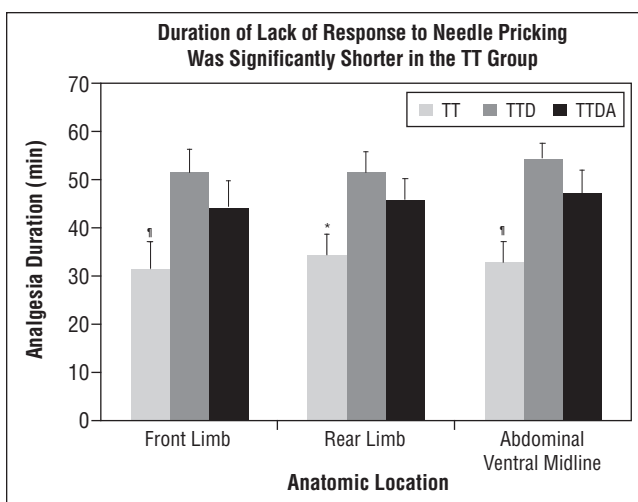
lower recovery quality scores in TTDA dogs versus the TTD group, though not statistically significant, further support this explanation. It is also possible that the reversal of medetomidine eliminated the muscle-relaxant effect of this drug, resulting in a rougher recovery. Based on these results, it can be concluded that the administration of atipamezole 60 minutes after TTD at these dosages was ineffective and, thus, is not recommended.

There was a significant difference in recovery quality score between TT and the other two treatment groups. Dogs in the TT group had a less optimal recovery score than did dogs in either the TTD or TTDA group. TT-treated dogs attempted sternal recumbency and standing more frequently. In addition, some dissociative recovery signs were observed, including head shaking and tongue flicking, which was attributed to residual tiletamine ef-

fects. The reported metabolic half-lives of tiletamine and zolazepam in dogs are 1.3 and 1 hour, respectively.<sup>13</sup> The shorter metabolic half-life of zolazepam likely allowed dissociative actions to be evident during recovery. Collectively, the addition of medetomidine to the TT combination (TTD) improved analgesia and reduced the dose requirement of tiletamine–zolazepam from 5 to 3 mg/kg. Thus, the rougher recovery associated with tiletamine would be lessened by dose reduction with the TTD and TTDA treatments.

The addition of medetomidine increased blood pressures in the TTD- and TTDA-treated dogs compared with the TT-treated dogs. This is not a surprise since medetomidine's vasoconstriction effect via  $\alpha_2$ -adrenoreceptor activity has been well documented.<sup>14–21</sup> DAP was significantly lower in the TT group at baseline compared with the TTDA group. It is possible that this contributes to the observation that DAP was significantly lower in the TT group through the 40-minute evaluation point. Although there was not an observed difference in baseline blood pressures between the other treatment groups, it is notable that baseline blood pressures were somewhat high in all dogs. SAP dropped in the TT dogs following drug administration, while MAP and DAP did not change significantly from baseline. The reflex bradycardia associated with vasoconstriction was not observed consistently and occurred in only three dogs during the first 5 minutes in the TTA and TTDA groups. Further episodes of reflex bradycardia were likely prevented by the co-administration of glycopyrrolate. Fur-

#### Duration of Lack of Response to Needle Pricking Was Significantly Shorter in the TT Group



**Figure 5.** Analgesia evaluation via needle prick following IM administration of tiletamine–zolazepam–butorphanol (TT), tiletamine–zolazepam–butorphanol–medetomidine (TTD), and tiletamine–zolazepam–butorphanol–medetomidine reversed with atipamezole (TTDA) in seven dogs. All data are presented as mean  $\pm$  SEM. \*Significantly different from other treatments. ‡Significantly different from TTD.

thermore, tiletamine likely contributes a positive chronotropic effect by increasing the HR in these dogs similar to ketamine-induced increases in HR seen in medetomidine-sedated dogs.<sup>22,23</sup>

Glycopyrrolate was used in all three treatment groups for the purpose of preventing bradycardia induced by medetomidine as well as reducing the salivation induced by tiletamine.<sup>24–26</sup> One initial concern was that the administration of glycopyrrolate may induce tachycardia by exacerbating a higher HR in the TT group. However, results showed that none of the dogs had tachycardia after receiving tiletamine and glycopyrrolate. Although a combination of tiletamine and glycopyrrolate did prevent most episodes of bradycardia, three dogs had an HR lower than 60 bpm during the first 5 minutes after TTD or TTDA administration. HR increased when glycopyrrolate

started to take effect. This delayed response of anticholinergics has been previously observed and reported when combined with medetomidine in dogs.<sup>26</sup>

RRs decreased in the TT and TTDA groups but not in the TTD group. Baseline RR for the TTD group was significantly lower than baseline RR in the other groups. This may be why no decline in RR was seen over time in the TTD group. All three treatments had a significant effect on PaO<sub>2</sub>, which decreased significantly from baseline after all drug treatments. A recent study reported transient hypoxemia in dogs administered tiletamine–zolazepam, with more severe hypoxemia observed in animals receiving the drugs IV.<sup>27</sup> That study used higher doses of tiletamine–zolazepam, and transient hypercarbia was also observed.<sup>27</sup> Two dogs in

benefited tissue oxygenation in treated dogs versus dogs breathing room air. Based on this information, it is advised that 100% oxygen via face mask insufflation or endotracheal intubation be available when using TT or TTD combinations.

Plasma lactate concentration has been used to monitor tissue perfusion and tissue oxygenation and hypoxia.<sup>29</sup> Normal blood lactate concentration in dogs is suggested to be less than 2.5 mmol/dl; values between 5 and 7 mmol/dl are considered moderately elevated, and values above 7 mmol/dl are considered severely elevated.<sup>29</sup> In this study, all lactate concentrations obtained from arterial samples were less than 2.5 mmol/dl at all times, indicating that none of the three injectable anesthetic combinations caused hyperlactatemia.

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***It was a surprise that the administration of atipamezole did not significantly shorten recovery time.***

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the current study had PaO<sub>2</sub> values below 60 mm Hg following both TTD and TTDA administration. The reduction of PaO<sub>2</sub> and arterial hemoglobin saturation with oxygen in the treated dogs was not likely entirely due to hypoventilation because PaCO<sub>2</sub> was within the normal range in all dogs, despite lower RRs in two of the groups. Medetomidine administration results in increased peripheral vasoconstriction and increased venous desaturation via an increase in peripheral tissue oxygen extraction.<sup>28</sup> A decrease in PaO<sub>2</sub> was also seen in the TT group, which did not receive medetomidine. More work needs to be done to evaluate the effects that multiple-drug injectable combinations have on blood and tissue oxygen levels. In a recent study,<sup>28</sup> medetomidine-sedated dogs were provided 100% oxygen via face mask insufflation, which increased oxygen content and

The baseline lactate concentration in the TT group was higher than the baseline values in the other groups but was still within the normal reference range. The reason for the higher baseline in the TT group is unknown; however, the drop in lactate observed in the this group over time may be a reflection of the higher baseline values. All other blood gas values were within normal limits in all dogs.

The duration of analgesia was approximately 35 minutes for TT-treated dogs and 50 minutes for TTD- and TTDA-treated dogs. In this study, the hypothesis that TTD would provide a longer duration of anesthesia and better quality of analgesic effects than TT was accepted. In the TT combination, butorphanol provides more analgesia to the dissociative anesthetic; however, when medetomidine was added to this combination (TTD), medetomidine likely

induced greater analgesia to the injectable combination.<sup>6,30</sup> The analgesic activity of these combinations was well demonstrated in that the algometer and nerve stimulator readings were all significantly higher in the TTD and TTDA groups than in the TT group in all anatomic testing locations between 5 and 50 minutes after drug administration. The addition of medetomidine also extended the analgesic duration for an additional 10 minutes in TTD- and TTDA-treated dogs compared with TT-treated dogs. Besides increasing analgesia, medetomidine also augmented central nervous system depression in the TTD-treated dogs and significantly increased the duration of intubation tolerance and lateral recumbency.

In this study, three modes of noxious stimulation were used to test analgesic effect: an algometer for testing the animal's response to pressure for deep pain; a nerve stimulator to test the animal's response to electrical noxious stimulation; and needle pricking to test the animal's somatic analgesia. While the duration of analgesia varies slightly with each type of noxious stimulus, TT produced a shorter duration of effect than did TTD and TTDA when using all three methods of analgesic assessment. The use of an algometer and nerve stimulator allowed differentiation of the degree of analgesia induced by each drug combination. The animals given TTD and TTDA tolerated a higher pressure and increased electrical stimulation than was observed following TT administration to these same seven dogs.

## ■ CONCLUSION

In conclusion, the anesthetic duration of these three combinations was approximately 50 to 60 minutes, with analgesic durations of 35 to 50 minutes. Cardiorespiratory changes were characterized by mild transient hypertension and occasional bradycardia when medetomidine was given. Transient mild hypoxia was

observed in some dogs, and providing 100% oxygenation is recommended. Reversal of medetomidine with atipamezole 60 minutes after TTD injection was not effective in shortening the recovery duration and is not recommended in TTD-treated dogs.

## ■ ACKNOWLEDGMENTS

The authors thank Constance Nickline and Meghan McMonagle for their technical assistance with this study.

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