

ANAESTHETIC EFFECTS OF XYLAZINE COMBINATIONS IN HIGH AND LOW CONCENTRATIONS OF TILETAMINE-ZOLAZEPAM, WITH AND WITHOUT KETAMINE, IN CATS

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SUMMARY

Intramuscular (IM) administration of four anaesthetic combinations were evaluated on nine cats in a repeated manner. The anaesthetic regimens were: (i) 2 mg/kg tiletamine, 2 mg/kg zolazepam, 3.2 mg/kg ketamine and 0.8 mg/kg xylazine (T₄KX); (ii) 1 mg/kg tiletamine, 1 mg/kg zolazepam, 3.2 mg/kg ketamine and 0.8 mg/kg xylazine (T₂KX); (iii) 2 mg/kg tiletamine, 2 mg/kg zolazepam and 0.8 mg/kg xylazine (T₄X); and (iv) 1 mg/kg tiletamine, 1 mg/kg zolazepam and 0.8 mg/kg xylazine (T₂X). All four combinations induced smooth recumbency within 4 minutes following IM administration and enabled intubation. All four anaesthetic combinations caused an immediate increase in heart rate and a dramatic decrease in respiratory rate. Pale to slight cyanotic mucous membrane was observed in most cats, 5 minutes following administration of any of the anaesthetic combinations. The T₄KX combination provided the longest duration of anaesthesia, followed by T₂KX, T₄X and T₂X. Time from IM injection to righting reflex, sternal recumbency, and standing or walking, was longest after administration of T₄KX, followed by T₄X, T₂X and T₂KX. Quality of recovery from anaesthesia was better following T₂X and T₂KX administration compared to T₄X and T₄KX. This study demonstrates the benefits of adding ketamine in the anaesthetic combination to reduce the tiletamine-zolazepam component. The data in this study can be used to compare and choose an initial IM TKX induction dose for short and non-invasive procedures in cats.

Keywords: Injectable anaesthetic, tiletamine-zolazepam, ketamine, xylazine, cat

INTRODUCTION

Tiletamine and zolazepam is a proprietary combination, and available as Zoletil® (Virbac Pty Ltd, NSW, Australia) or Telazol® (Fort Dodge Lab., IA, USA). The use of this combination, either alone, or with other anaesthetics or adjuncts, has been described in cats, dogs, horses, ruminants, exotic and wildlife species (Lin, 1996). Intravenous (IV) and intramuscular (IM) administration of this commercial tiletamine and zolazepam combination (T) have routinely been used in both dogs and cats for minor procedures not lasting longer than 45 – 60 minutes at the Universiti Putra Malaysia Veterinary Hospital. The typical practice involves an initial IV dose of 5 mg/kg and a top up of 1/3 – 1/2 of the initial IV dose when needed. Often, at least a top-up dose is needed to complete a short procedure such as a cat orchietomy by a senior veterinary student. Recovery is usually calmer with less movement and vocalisation in cats than in dogs, although some cats exhibit ataxia and repeated falling in the cage (Chen, pers. comm.; Tracy *et al.*, 1988).

The use of T at a dose rate of 15 mg/kg (7.5 mg/kg tiletamine and 7.5 mg/kg zolazepam), IM, induced satisfactory anaesthesia for ovarietomy, with anaesthesia time lasting approximately 50 minutes (Verstegen *et al.*,

1991). However, there were significant pain reactions on injection, and recovery was often violent. Only 50% of the cats in the above study had good muscle relaxation. This led to the idea of adding other anaesthetics and adjuncts, such as ketamine and xylazine that may improve the quality of induction, muscle relaxation and recovery.

Ko *et al.* (1993) have described the use of tiletamine-zolazepam-ketamine-xylazine (TKX) for onychectomy and orchietomy in cats. The TKX mixture was prepared by adding 4 ml of ketamine (100 mg/ml) and 1 ml of xylazine (100 mg/ml) into a vial of lyophilized Telazol® (250 mg tiletamine and 250 mg zolazepam). Hence, each ml of the reconstituted combination contained 50 mg tiletamine, 50 mg zolazepam, 80 mg ketamine and 20 mg xylazine. The mixture was administered at 0.015 ml/lb (or 0.033 ml/kg), IM, together with 0.02 mg/lb atropine. Essentially, this means that each component of the TKX mixture was administered in the following dose rate: 1.65 mg/kg tiletamine, 1.65 mg/kg zolazepam, 2.64 mg/kg ketamine and 0.66 mg/kg xylazine. The study reported that the TKX combination provided rapid and smooth induction enabling intubation. It produced excellent muscle relaxation, with anaesthesia lasting for about 40 minutes. Recovery was smooth. The mixture also has

the advantage of a small injection volume, thus facilitating the IM injection and reducing pain reactions.

In 2002, Williams *et al.* described the use of TKX combination for large-scale cat neutering clinics that involved 7,502 feral cats. The mixture was prepared as described by Ko *et al.* (1993), but administered at a higher IM dose of 0.25 ml per adult cat (mean weight of 3.04 ± 0.8 kg). In other words, the dose rate for each component of the TKX mixture was approximately 4.11 mg/kg tiletamine, 4.11 mg/kg zolazepam, 6.58 mg/kg ketamine and 1.64 mg/kg xylazine. This higher dosage enabled placement of the identification tag, removal of the tip of the left ear, vaccinations, medications for internal and external parasites and surgery (ovariohysterectomy and orchietomy) to be performed in pregnant or non-pregnant females, as well as normal or cryptorchid males. When necessary, additional top-up doses (0.05 – 0.25 ml) were administered to achieve sufficient anaesthetic depth. This combination was found to be inexpensive, provided predictable results, could be administered quickly and easily in small volume, and associated with a low mortality rate in feral cats. The mortality rate attributable solely to potential anaesthetic deaths in this study was only 0.23% (17/7,502 cats), which was comparable to other studies, despite the large scale nature of the clinics. Furthermore, these feral cats had unknown history, no prior physical examination or laboratory evaluation, poor body condition in some, and were often highly stressed prior to anaesthesia.

Based on the study by Williams *et al.* (2002), the TKX mixture at the described higher dose rate could be a promising anaesthetic combination alternative for small animal practitioners in Malaysia. It is also especially relevant for stray cats neutering campaign, where facilities to administer an inhalant anaesthetic in the field are usually not available. For short procedures such as orchietomy, superficial wound debridement and suturing, or restraint for radiography in an otherwise healthy cat, a lower dose rate such as that described by Ko *et al.* (1993), or even lower, may be more appropriate. Reviewing the cost for each component of the TKX mixture, tiletamine-zolazepam contributed to about 75% of the cost. Thus, it may be more sensible to reduce the T component when lesser duration or anaesthetic effect is required. Question on the benefit of having ketamine in the TKX mixture also arose, since tiletamine (also a dissociative agent like ketamine) is already present in the mixture. This paper aims to describe and compare the duration of anaesthetic effects of the TKX mixture at half the dose rate described by Williams *et al.* (2002), the effect of halving the T concentration, and the absence of ketamine from these combinations.

MATERIALS AND METHODS

Experimental animals

Nine domestic short haired cats, 8 months to 5 years of age, 2.1 to 5.25 kg body weight were used to test all four anaesthetic combinations, with a wash-out period of 4 days between experiments. They were judged to be healthy based on physical examination. They were housed in individual cages and provided dry food and water *ad libitum*. Cats were fasted for 12 hours prior to each experiment.

Anaesthetic combinations

The dose rate for each component of the TKX mixture in the study by Williams *et al.* (2002) was approximately 4.11 mg/kg tiletamine, 4.11 mg/kg zolazepam, 6.58 mg/kg ketamine and 1.64 mg/kg xylazine. Therefore, to study the effect of TKX mixture at half the dose rate described by Williams *et al.* (2002), the effect of halving the T concentration, and the absence of ketamine from these combinations, the dose rate evaluated in this study were as follows:

- (i) 2 mg/kg tiletamine with 2 mg/kg zolazepam (4 mg/kg T), 3.2 mg/kg ketamine and 0.8 mg/kg xylazine (T₄KX).
- (ii) 1 mg/kg tiletamine with 1 mg/kg zolazepam (2 mg/kg T), 3.2 mg/kg ketamine and 0.8 mg/kg xylazine (T₂KX).
- (iii) 2 mg/kg tiletamine with 2 mg/kg zolazepam (4 mg/kg T) and 0.8 mg/kg xylazine (T₄X).
- (iv) 1 mg/kg tiletamine with 1 mg/kg zolazepam (2 mg/kg T) and 0.8 mg/kg xylazine (T₂X).

The first anaesthetic combination was prepared by adding 2.0 ml of ketamine 100 mg/ml ketamine Ketavet 100[®], DELVET Pty Ltd.) and 0.5 ml of 100 mg/ml xylazine (Xylazil 100[®], TROY Lab Pty Ltd.) into a vial of Zoletil 50 which contained 125 mg tiletamine and 125 mg zolazepam. Consequently, each millilitre of this mixture contained 50 mg of tiletamine, 50 mg of zolazepam, 80 mg of ketamine and 20 mg of xylazine. The dosage of this combination was 0.04 ml/kg (that is, 0.12 ml per a 3 kg cat, is approximately half the volume used by Williams *et al.*, 2002).

The second anaesthetic combination was prepared by placing 0.75 ml of the first anaesthetic mixture into a sterile empty vial followed by 0.60 ml of 100 mg/ml ketamine and 0.15 ml of 100 mg/ml xylazine. Thus, each millilitre of this mixture contained 25 mg of tiletamine, 25 mg of zolazepam, 80 mg of ketamine and 20 mg of xylazine. The dosage for this combination was 0.04 ml/kg.

The third anaesthetic combination was prepared by adding 2.0 ml of the provided diluent and 0.5 ml of 100

mg/ml xylazine into a vial of Zoletil 50. Thus, each millilitre of this mixture contained 50 mg tiletamine, 50 mg zolazepam and 20 mg xylazine. The dosage for this combination was 0.04 ml/kg.

The fourth anaesthetic combination was prepared by adding 0.75 ml of the third anaesthetic mixture into a sterile empty vial followed by 0.60 ml of the provided diluent and 0.15 ml of 100mg/ml xylazine. Each millilitre of this mixture contained 25 mg tiletamine, 25 mg zolazepam and 20 mg xylazine. The dosage for this combination was 0.04 ml/kg.

Atropine sulphate (Atrosite, TROY Lab Pty Ltd.) at the dosage of 0.05 mg/kg was withdrawn and mixed into the same syringe with the TKX mixtures immediately prior to the IM administration.

Experimental protocols

Each cat was tested with all four anaesthetic combinations in a repeated manner, with a four-day wash-out period between each anaesthetic combinations. Prior to induction, baseline heart rate, respiratory rate and rectal temperature were determined. The drugs were administered intramuscularly into the quadriceps muscle and pain reactions were noted. After injection, the cats were placed into a box and were monitored until they became recumbent. Following recumbency, mucous membrane colour, palpebral reflexes and jaw tone were examined. Intubation was attempted when the jaw was judged to be sufficiently relaxed. The cat was then placed on left lateral recumbency. Heart rates were counted manually by auscultation of the chest with a stethoscope. Respiratory rates were counted based on observation of the chest excursion. Both heart rate and respiratory rate were determined before application of the noxious stimuli, and at 5-minute intervals following the IM injection until the cat resumed sternal recumbency. Rectal temperature was monitored using a digital thermometer every 30 minutes for 5 hours.

Pedal reflex was elicited every 5 minutes by pinching the interdigital toe web of the right hind foot. Superficial noxious stimulus was simulated by clamping a fold of skin at the ventral mid-abdominal region, and the perineal region with an Allis tissue forcep clamped at the level of one rachet. Deeper noxious stimulus was simulated by using the handle of the forcep to clamp a coccygeal vertebra at the level of one rachet. Noxious stimuli were applied for 10 seconds each, in the order of abdominal skin clamp, perineal clamp and tail clamp every 5 minutes. Stimuli were removed and discontinued when positive response was observed. Positive responses were defined to include purposeful movement of tail or legs, lifting of head, swallowing or vocalisation.

Time from injection to recumbency, intubation, return of positive response to noxious stimuli, return of pedal reflex, return of righting reflex, sternal recumbency and

standing were determined for each cat. Duration of intubation was taken as the time of intubation until the cat showed coughing reflex or swallowing reflex for the first time. Quality of recovery was scored from 1 to 5, with the higher score indicating better recovery (Appendix 1).

Statistical Analysis

Duration of anaesthetic effects was analysed for difference in treatment using one-way analysis of variance (ANOVA) and post-hoc Duncan's multiple range test. Heart rate, respiratory rate and rectal temperature were evaluated for difference from baseline values using ANOVA and post-hoc Dunnett's test. A p-value of < 0.05 was considered significant.

RESULTS

All four anaesthetic combinations caused mild to strong vocalisation upon IM injection. Retching occurred in 2, 4, 3 and 7 cats following administration of T₄KX, T₂KX, T₄X and T₂X respectively. All four combinations induced smooth recumbency within 4 minutes following IM administration, with no signs of excitement. T₄KX and T₂KX induced recumbency more rapidly than T₂X, while a significant difference was not visible between T₄X and T₂X (Table 1).

Pale to cyanotic mucous membrane was observed in 83% of the cats at 5 minutes following IM injection of all anaesthetic combinations. At 10 minutes, 67% of cats treated with T₄KX and T₂KX still showed pale to cyanotic mucous membrane while 67% of T₂X and 89% of T₄X-treated cats showing pink mucous membrane. At 5 minutes, strong palpebral reflex was elicited in cats treated with T₂X while T₂KX, T₄X and T₄KX treated cats showed slight palpebral reflex.

Tracheal intubation could be carried out in all cats following IM administration of all four anaesthetic combinations. The time from injection to the ability to intubate ranged from 4 to 5 minutes for all four combinations. There was no significant treatment difference in the duration of intubation.

All four treatments caused an immediate increase in heart rate following IM injection, gradually decreasing to baseline by the time of sternal recumbency. All treatments caused an immediate and dramatic decrease in respiratory rate following anaesthetic administration, which gradually increased to baseline values as cats recovered. Apneustic breathing pattern was observed within 10 minutes following all four regimens. Rectal temperature dropped to the lowest level of 36°C and did not increase above 37°C within the 5 hours of observation.

T₄KX provided the longest duration of action, as measured by the time from injection to positive response

Table 1: Duration of anaesthetic effects following intramuscular injection of xylazine (X) combinations at high and low concentration of tiletamine-zolazepam (T), with and without ketamine (K).

Parameters	T ₄ KX	T ₂ KX	T ₄ X	T ₂ X
TI to recumbency	2.59 ± 0.09 ^a	2.61 ± 0.12 ^a	2.72 ± 0.13 ^{ab}	3.10 ± 0.21 ^b
TI to intubation	4.30 ± 0.33 ^a	3.84 ± 0.19 ^a	4.23 ± 0.26 ^a	4.34 ± 0.30 ^a
Duration of intubation	39.06 ± 10.75 ^a	24.10 ± 3.99 ^a	29.28 ± 4.30 ^a	21.50 ± 2.93 ^a
TI to abdominal skin clamp response	59.42 ± 4.75 ^b	42.64 ± 2.44 ^a	44.13 ± 2.31 ^a	34.56 ± 3.85 ^a
TI to perineal clamp response	48.07 ± 3.90 ^c	34.58 ± 1.12 ^b	33.12 ± 3.44 ^b	21.51 ± 2.35 ^a
TI to tail clamp response	43.83 ± 2.80 ^c	32.18 ± 1.47 ^b	29.90 ± 2.26 ^b	16.51 ± 2.12 ^a
TI to pedal reflex	46.40 ± 5.81 ^b	40.05 ± 4.38 ^{ab}	35.06 ± 3.59 ^{ab}	27.15 ± 2.86 ^a
TI to righting reflex	67.61 ± 6.89 ^b	49.20 ± 3.74 ^a	54.62 ± 3.28 ^{ab}	50.59 ± 6.39 ^a
TI to sternal recumbency	71.15 ± 7.78 ^b	51.32 ± 3.76 ^a	56.73 ± 3.69 ^{ab}	53.71 ± 4.36 ^a
TI to standing/walking	76.46 ± 8.30 ^b	56.86 ± 3.96 ^a	58.36 ± 3.49 ^a	55.31 ± 4.30 ^a

Data are expressed as mean ± standard error, n = 9.

Values with different superscripts differ significantly (p < 0.05).

TI - time (minute) from injection

T₄KX - 2 mg/kg tiletamine with 2 mg/kg zolazepam, 3.2 mg/kg ketamine and 0.8 mg/kg xylazine.

T₂KX - 1 mg/kg tiletamine with 1 mg/kg zolazepam, 3.2 mg/kg ketamine and 0.8 mg/kg xylazine.

T₄X - 2 mg/kg tiletamine with 2 mg/kg zolazepam and 0.8 mg/kg xylazine.

T₂X - 1 mg/kg tiletamine with 1 mg/kg zolazepam and 0.8 mg/kg xylazine.

to abdominal skin clamp, perineal clamp and tail clamp (Table 1). No differences were observed between T₂KX and T₄X, while T₂X provided the shortest duration of action. A similar trend was observed in the time of injection to return of pedal reflex.

The time from injection to righting reflex was longest following administration of T₄KX, followed by T₄X, T₂X and T₂KX. Similar trends were observed in the time from injection to sternal recumbency and standing/walking. The majority of the cats showed good and quiet recovery following T₂KX (78% scored 3) and T₂X (44% scored 4). Cats were more ataxic and made more attempts to stand following T₄KX (78% scored 2) and T₄X (89% scored 2).

DISCUSSION

This study describes the effect of IM administration of T₄KX at approximately half the dose rate used by Williams *et al.* (2002), the effect of reducing the T concentration to half (T₂KX), and the absence of ketamine from the mixtures (T₄X and T₂X). This study demonstrates that all four anaesthetic combinations can be administered IM to achieve rapid recumbency within 4 minutes. All four combinations provided adequate jaw relaxation and anaesthetic depth to enable tracheal intubation that lasted for at least 21.5 ± 8.78 minutes, which is the shortest duration of anaesthesia, following T₂X.

All four combinations induced anaesthesia that enabled painful procedures equivalent to tail clamping to be carried out for at least 16.51 ± 6.35 minutes (the

shortest duration, following T₂X), to as long as 43.83 ± 8.4 minutes (the longest duration, following T₄KX). Reducing the T concentration to half (T₂KX) or absence of ketamine from the mixture (T₄X) decreased the duration of action (absence of positive response to noxious stimuli) to the same degree in both combinations. Time to righting reflex and sternal recumbency were significantly decreased by reducing the T concentration (T₂KX and T₂X), but not in the absence of ketamine (T₄X). These results suggest that the addition of 3.2 mg/kg ketamine to T₂X has the advantage of providing a similar duration of anaesthetic effect to that of doubling the T concentration to T₄X, without increasing the time to recovery. Furthermore, the quality of recovery was better following T₂KX and the cost is also lower when compared to T₄X (Appendix 2).

The poorer recovery score and tendency for longer recovery time in both T₄X and T₄KX was likely due to the higher dosage of tiletamine and zolazepam in these regimens compared to T₂KX and T₂X treatments. The recovery time in cats is known to be prolonged due to the longer plasma half-life of tiletamine and zolazepam in cats (Lin, 1996). The presence of ketamine in T₂KX may have added to the initial anaesthetic effect, thus providing an equivalent duration of effective anaesthetic effect as in T₄X treatment. However, since the action of ketamine is shorter than tiletamine (Lin, 1996), this probably explain the short recovery time using T₂KX. This further supports the advantage of adding ketamine to reduce the T component in the mixture.

The pale to slight cyanotic mucous membrane observed in some of the cats during the first 5 – 10 minutes

following anaesthetic administration is likely a reflection of vasoconstriction caused by xylazine, and possibly respiratory depression caused by the combined effects of xylazine, tiletamine and ketamine. A similar side effect was also reported in a study using the TKX mixture at a dose rate double that of T₄KX, where haemoglobin saturation (SpO₂) fell below 90% at least once in 88% of female cats (Cistola *et al.*, 2004). Decreased SpO₂ values could be due to vasoconstriction, low inspiratory oxygen tension (breathing of room air), hypoventilation, ventilation-perfusion mismatched or shunting. Since cats in the present study and that by Cistola *et al.* (2004) were breathing room air, oxygen supplementation may have helped to correct this side effect. In our study, the greatest respiratory depression was observed during the initial anaesthetic period, indicating greater central nervous depression. Perhaps, a lower induction dosage of TKX may reduce the respiratory depression; however this practice would likely require more topping up of TKX to maintain anaesthesia.

The increased heart rate following drug administration could be due to sympathetic stimulation by the pain from IM injection, tiletamine and ketamine, as well as the vagolytic effect of atropine. The cardiovascular stimulating effect of tiletamine and ketamine are well known (Tracy *et al.*, 1988; Hellyer *et al.*, 1988; Lin, 1996), however, a significant increase in heart rate was not documented in previous studies on TKX combination (Ko *et al.*, 1993; Cistola *et al.*, 2004). An anticholinergic drug was not used in the study by Cistola *et al.* (2004) and increase heart rate was not observed. Atropine was included in our anaesthetic protocol with the intention of controlling ptialism. Since significant and sustained tachycardia was observed in the present study, it is advisable not to administer atropine routinely in clinical cases, but to reserve for use only when necessary. This would also reduce the volume of drug to be injected and may help to reduce the pain reactions associated with the IM injection.

Body temperature decreased significantly in all cats following all four anaesthetic mixtures, indicating the loss of ability to regulate temperature during general anaesthesia (Harvey, 2002). However, the drop in temperature was not excessive (> 36%), and should not inflict a significant detrimental effect.

This study was limited by the fact that the noxious stimuli were simulated using skin and tail clamp, and not by actual surgery. Actual skin incisions and surgical procedures may provide more realistic descriptions of the utility of the anaesthetic regimens. Nevertheless, the results of this study can be used as a guide to compare

and choose the initial TKX dosage for short and non-invasive procedures. This study also demonstrates the benefits of adding ketamine to reduce the T concentration, and the utility of all four combinations as induction agents that enable intubation. Future studies should be designed to evaluate their utility in clinical cases involving actual procedures.

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Appendix 1: Descriptions for scoring quality of recovery

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- 1 – Violent excitement
 - 2 – Ataxic before standing, several attempts to rise, very ataxic once standing
 - 3 – Quiet recovery, several attempts to stand, ataxic when standing or walking
 - 4 – Good, quiet recovery, stand on first attempt, mild ataxia when standing or walking
 - 5 – Good, quiet recovery, stand on first attempt, no ataxia when standing or walking
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Appendix 2: Cost of anaesthetics per kg body weight

Anaesthetic component	T ₄ KX	T ₂ KX	T ₄ X	T ₂ X
Tiletamine -zolazepam (T)	RM 0.64	RM 0.32	RM 0.64	RM 0.32
Ketamine (K)	0.10	0.10	-	-
Xylazine (X)	0.05	0.05	0.05	0.05
Total cost per kg body weight	0.79	0.47	0.69	0.37

Note: Calculation of cost based on price list as of October 2005.