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Comparison of Intranasal and Intramuscular Administration of Zolazepam-Tiletamine Combination in Cats

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Absract: The purpose of the current study was to compare intranasal (IN) and intramuscular (IM) administration of zolazepam-tiletamine (ZT) combination in cats. Eight adult healthy cats weighing 2.47 ± 0.6 kg were used. Each animal received 10 mg/kg ZT combination by IN and IM routes with a minimum one week intervals. The onset of sedation, the length of surgical anaesthesia and the recovery time were recorded. The parameters were recorded immediately before and at 5, 10, 15, 20, and 30 min after administration of ZT combination. No anaesthetic complication was observed in either administration route. Recovery was uneventful in all animals. There were no statistical differences between the IN and IM administration with respect to onset of sedation and the length of anaesthesia. Recovery time was significantly shorter when the ZT combination was administered IN route (30.63 ± 0.32 min) compared to IM injection (33.38 ± 0.32 min). The route of administration of the ZT combination had no effect on heart rate (P = 0.388), respiratory rate (P = 0.628), rectal temperature (P = 0.066), and peripheral haemoglobin oxygen saturation (P = 0.442). Intranasal administration of ZT combination can be an alternative technique for sedation in cats.

Keywords: Anaesthesia, Cat, Intramuscular, Intranasal, Tiletamine, Zolazepam.

Kedilerde İntranasal ve İntramusküler Zolazepam-Tiletamine Kombinasyonu Uygulamasının Karşılaştırılması

Öz: Bu çalışmanın amacı kedilerde zolazepam-tiletamine (ZT) kombinasyonunun intramusküler (IM) ve intranasal (IN) uygulamasını karşılaştırmaktı. Ağırlıkları 2.47 ± 0.6 kg olan 8 sağlıklı erişkin kedi kullanıldı. Her kediye 10 mg/kg ZT kombinasyonunu uygulamalar arasında en az birer hafta ara olacak şekilde IN ve IM yol ile verildi. Sedasyon başlangıcı, cerrahi anestezi süresi ve uyanma zamanı kaydedildi. Parametreler ZT kombinasyonundan hemen önce ve uygulama sonrasındaki 5, 10, 15, 20 ve 30. dakikalarda kaydedildi. Her iki uygulama yolunda, herhangi bir anestezik komplikasyon görülmedi. Tüm hayvanlarda uyanma problemsiz gerçekleşti. Anestezi süresi ve sedasyon başlangıcı değerleri, IN ve IM uygulamaya bağlı istatistiksel farklılık göstermedi. ZT kombinasyonu IN yolla verildiğinde (30.63 ± 0.32 dakika) IM enjeksiyona (33.38 ± 0.32 min) göre istatistiksel olarak daha kısa sürede uyanma gerçekleşti. ZT kombinasyonun uygulama yolunun, kalp frekansı (P = 0.388), solunum sayısı (P = 0.628), rektal sıcaklık (P = 0.066) ve peripheral hemoglobin oksijen saturasyonu (P = 0.442) değerleri üzerine etkisi yoktu. ZT kombinasyonunun intranasal uygulanması kedilerde sedasyon için alternatif bir teknik olabilir.

Anahtar Kelimeler: Anestezi, Intranasal, Intramusküler, Kedi, Tiletamine, Zolazepam.

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INTRODUCTION

Zoletil or Telazol, combination of equal volume of zolazepam hydrochloride and tiletamine hydrochloride, has been used in veterinary patients for immobilization and minor surgical procedures due to its rapid anaesthetic action (1). Adverse effects of combination include salivation, muscle rigidity, hypothermia, respiratory depression, tachycardia, and a prolonged recovery time (2, 3).

Intravenous drug administration is less preferred route of administration than intramuscular (IM) injection in cats due to necessity of placing an intravenous catheter (4). However, IM injection of zolazepam-tiletamine (ZT) combination results with pain response in animals due to its low pH (5). Intranasal administration of ZT combination has been reported in a lynx for wound treatment (6) and cats for its effect on intraocular pressure (7).

The goal of the current study was to compare the effects of IN and IM administration of ZT combination on time to onset of sedation, length of surgical anaesthesia and recovery time.

MATERIALS and METHODS

Animals: This study has been approved by Atatürk University Local Board of Ethics Committee for Animal Experiments, Erzurum, Turkey (decision no: 2016/119). Eight healthy mixed-breed owned cats aged 3 years (four males and four females, mean weight 2.47 ± 0.6 kg SD) were used in this study. Client consent was obtained for each cat before the intervention. Prior to the experiment, the animals were underwent complete physical examination, thoracic x-ray and blood tests. Food, but not water, was withdrawn 12 hours prior to the anaesthesia.

Study design: Each animal (n=8) randomly received 10 mg/kg ZT combination (Zoletil-50, Virbac, Carros Cedex, France) by IN and IM routes with a minimum one week washout periods. The sterile saline was added to the ZT combination to reach the final volume of 1 mL for both administrations. For IN administration, the prepared solution was administered equally (0.5 mL each) into the medial wall of each nasal cavity by using a 16 G intravenous catheter that attached to the insulin syringe (Figure 1). The catheter was inserted into the each nostril no more than 0.5 cm for possible damage in the caudal nasal cavity. During the each IN administration, the animal was gently restrained by an assistant, and the animal's head was held upward for 5 seconds. For IM administration, the prepared solution was administered into the quadriceps femoris muscle. Following the administration in both groups, the cats were placed on an examination table, and no noxious stimulation was applied throughout the anaesthesia.

Figure 1. Intranasal administration of zolazepam-tiletamine combination.
Şekil 1. Zolazepam-tiletamine kombinasyonun intranasal uygulaması.

Onset of sedation was defined as the time from administration of drug to the time of when the animal became lateral recumbent. The length of

anaesthesia was determined as the time from lateral recumbency to the time of first head movement. Recovery was defined as the time from first head movement to time standing on its own.

Measurements: The heart rate (HR), respiratory rate (RR) rectal temperature (RT) and peripheral haemoglobin oxygen saturation (SpO_2) were measured by a veterinary vital signs monitor (Cardell, 9404, Sharn Veterinary Inc, USA). The probe of SpO_2 was attached to the ear of cats. All measurements were recorded immediately before (T0; baseline) and at 5, 10, 15, 20, and 30 min after administration of ZT combination.

Statistical Analysis

Data were analyzed by one-way ANOVA. As the data were normally distributed, differences among mean values were treated with paired sample t-test. The effect of the route, time and the route by time interaction was considered significant at $P<0.05$. Data were presented as mean ± SD. SPSS 19.0 for Windows (IBM Company, SPSS Inc, USA, 2010) was used to evaluate the data.

RESULTS

IN administration of ZT combination resulted with a sneezing reaction in cats, whereas IM administration of ZT combination caused a vocalization. No anaesthetic complication was observed in both administration routes. Recovery was uneventful in all animals.

There were no statistical differences between two administration routes with respect to onset of sedation ($P=0.749$) and the length of anaesthesia ($P=0.621$). Recovery time was significantly shorter when the ZT combination was administered IN route (30.63 ± 0.32 min) compared to IM injection (33.38 ± 0.32 min) (Table 1).

Table 1. The effect of administration route of 10 mg/kg zolazepam-tiletamine combination on onset of sedation, length of surgical anaesthesia and recovery time.

Tablo 1. 10 mg/kg zolazepam-tiletamine kombinasyonu uygulama yolunun uyanma zamanı, sedasyon başlangıcı ve cerrahi anestezi süresi üzerine etkisi.

	Intranasal	Intramuscular	*P*
Onset of sedation (min)	5.63±0.54	5.88±0.54	0.749
Length of surgical anaesthesia (min)	11.13±0.70	11.63±0.70	0.621
Recovery time (min)	30.63±0.32	33.38±0.32	0.000

In both groups, HR increased following induction of anaesthesia and remained significantly elevated thereafter ($P<0.0001$). The RT ($P=0.04$) and SpO_2 ($P=0.042$) decreased following the anaesthesia. However, the RR did not significantly change with time (Table 2). The route of administration of the ZT combination had no effect on HR ($P=0.388$), RR ($P=0.628$), RT ($P=0.066$), and SpO_2 ($P=0.442$) (Table 2).

Table 2. Values for physiological data measured in cats administered 10 mg/kg zolazepam-tiletamine combination either by the intranasal or the intramuscular route. Time point 0 represents the baseline value. Data are presented as mean ± SD.

Tablo 2. Kedilere intranasal veya intramusküler yolla verilen 10 mg/kg zolazepam-tiletamine kombinasyonunda ölçülen fizyolojik verilerin değerleri. 0 zamanı uygulama öncesi değeri göstermektedir. Veri ortalama ± SD olarak sunulmaktadır.

PRM	RA	Time after treatment (min)						*P*- values		
		0	5	10	15	20	30	RA	T	RA*T
RR	IN	25±2	26±3	24±2	25±6	26±2	25±5	0.628	0.945	0.977
	IM	25±3	25±5	25±4	25±3	25±3	25±3	-	-	-
HR	IN	147±14[a]	187±21[b]	197±25[b]	198±17[b]	201±24[b]	205±26[b]	0.388	<0.0001	0.986
	IM	143±11[a]	183±16[b]	192±18[b]	195±23[b]	197±16[b]	201±18[b]	-	-	-
RT	IN	37.9±0.3[a]	37.3±0.5[b]	37.2±0.6[b]	37.3±0.8[b]	37.3±0.5[b]	37.1±0.2[b]	0.06	0.04	0.867
	IM	37.8±0.5[a]	37.3±0.4[b]	37.3±0.4[b]	37.1±0.3[b]	37.0±0.4[b]	37.0±0.7[b]	-	-	-
SpO_2	IN	96±4[a]	92±2[b]	92±5[b]	91±1[b]	92±3[b]	91±4[b]	0.442	0.042	0.942
	IM	95±2[a]	93±3[b]	92±3[b]	92±2[b]	91±3[b]	90±2[b]	-	-	-

RR (breaths per minutes): respiratory rate; HR (beats per minute): heart rate; RT (°C): rectal temperature; SpO_2(%): saturation of peripheral oxygen. PRM: parameter; IN: intranasal; IM: intramuscular. RA: route of administration; T: time; RA*T: interaction of administration route by time. [ab] Values with different superscripts within rows differ (P<0.05)

DISCUSSION and CONCLUSION

Zolazepam is in a group of benzodiazepine family that induces muscle relaxation and it is only available in combination with tiletamine, which is a member of cyclohexamine drug with a greater anesthetic potency and longer duration of action (8-11). The cyclohexamines causes an increase in HR due to increased catecholamine stimulation (1). In the current study, HR increased following the administration of ZT combination in both groups, which is consistent with previous study (3). In the present study RR did not change after the drug administration in both routes. Similar result was obtained when benzodiazepine and cyclohexamine combination has been used in cats (12). It has been stated that RT has tendency to decrease after administration of ZT combination due to muscle relaxation (13). In this study, RT decreased following the administration of ZT combination in both routes, which is consistent with previous report that used IM 2.5 mg/kg Zoletil in cats for sedation (14). In our study, SpO_2 value was not significantly different between groups. However, SpO_2 reduced following the administration of ZT combination in both groups. This finding suggests that the possible decrease in SpO_2 should be taken into account when ZT combination has been applied by either route.

In the current study, sneezing reaction was observed in cats following the IN administration of ZT combination which agreed with the previous study that used midazolam and ketamine combination with IN route in cats (12). In this study, the IM administration ZT combination caused a vocalization in cats possibly due to its acidic pH (5). Therefore, IN administration of ZT combination, which was easily applied and non-invasive, could be preferred for anaesthesia induction in cats.

We have previously reported that IN administration of ZT to the cats can be achieved with direct administration of drug into the each nostril of cat (7), however in this study, the nostril diameter of animals was not enough large to put the syringe into the inside of nostrils. We therefore decided to attach a catheter to the insulin syringe for safety administration of drugs. As a consequence, both methods of administrations may be used for IN drug delivery in cats while taking into consideration the nostril diameter to prevent the damage of nasal cavity.

The recommended dosage range for anaesthesia with ZT combination in cats is 5 to 15 mg/kg (2, 5, 15, 16). Because the dosage less than 5 mg/kg of ZT combination is not able to produce effective sedation in cats, additional drugs such as methadone (17) or butorphanol (18) should be consider. Moreover, it has been reported that ZT combination is not suitable for surgical procedures even it has been used at the 15 mg/kg dose in cats (16). In the current study, even though no noxious stimulation was applied to the cats for evaluating the surgical anaesthesia, administration of 10 mg/kg ZT combination either by IN or IM route produces effective sedation which lasts about 30 minutes. This finding was similar with a previous study that used ZT combination at a dosage of 5 mg/kg subcutaneously (2).

A previous study has reported that no significant difference has been observed between length of anaesthesia and time to recovery when the ZT was injected at the dose of 12.8mg/kg to cats by either IM or intravenous route (5). In the current study, the length of anaesthesia did not differ between two administration routes; however, recovery was more rapid in IN administration than in the IM administration group. This could be related to the well vascularized nature of nasal mucosa (19), which might have affected the rapid removal of anaesthetic from tissues or more likely the sneezing reaction might have resulted with losing some anaesthetic agent during the IN administration.

Because the IN drug delivery occurs through transmucosal absorption (20), future studies may also be needed to demonstrate the plasma drug concentrations, distribution and the plasma clearance of ZT combination when administered by the IN route. Additionally, a study that focused on the detailed examination of anaesthetic parameters may also needed to demonstrate the effectiveness of this technique. In conclusion, IN administration of ZT combination produces effective sedation in cats at the same dosage suggested for IM administration.

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