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Evaluation of Medetomidine Alone or in Combination with Tramadol on Tear Secretion in Cats and Their Reversal with Atipamezole

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ABSTRACT

To assess the effect of administration of medetomidine alone or in combination with tramadol on tear secretion (TS) in cats as well as their reversal with atipamezole. For the purpose of the study, a total of 46 cats, representing different breeds and genders, were selected and divided into two groups using a random assignment method. Group M was administered medetomidine at a dose of 80 µg/kg intramuscularly. Group MT was given a combination of medetomidine and tramadol at doses of 80 µg/kg and 2 mg/kg intramuscularly, respectively. Tear secretion was measured using Schirmer tear test I before sedation and at 15 (T_{15}) - 60 (T_{60}) minutes post-sedation with 15 min intervals. At 30 minutes, all cats were given atipamezole (200 µg/kg IM). TS statistically decreased until T_{30} measurement in both groups ($P < 0.05$). The TS decreased more in MT group compared to M group at T_{30} measurements ($P < 0.05$). TS increased in both groups post-atipamezole but didn't return to initial (T_0) levels by study end (T_{60}). Premedication with tear protectors or artificial tears is advised when using MT and M group agents in cats, and atipamezole can reverse their effects post-procedure.

INTRODUCTION

In various clinical examinations, such as ophthalmological and radiographic assessments, sedation may be necessary for animals. Although manual restraint is often adequate for conducting ophthalmic examinations in most cats, the use of sedatives and tranquilizers may be required in cases where the cat is particularly difficult to handle, in order to enhance the efficacy of the examination. By implementing an appropriate methodology, the stress levels related to the eye examination may be significantly reduced, while also guaranteeing the safety of both the patient and the examiner. Additionally, such a protocol would result in minimal alterations to ophthalmic variables (Dodam et al., 1998; Wolfran et al., 2022).

Alpha-2 adrenergic receptor agonists are effective in inducing sedation in cats for a variety of purposes, and possess the further benefit of being reversible with atipamezole. These pharmaceutical agents have the potential to be administered either as alone or in combination with an opioid (Tayari et al., 2015; Bruniges et al., 2016; Bhalla et al., 2018). The concomitant administration of an α_2-adrenergic receptor agonist and an opioid appears to potentiate the sedative and analgesic properties of the drugs while causing minimal additional cardiovascular effects (Selmi et al., 2003; Slingsby et al., 2010).

The administration of medetomidine, a selective α_2-adrenoceptor agonist, is commonly employed in veterinary medicine for sedation, analgesia, and muscle relaxation (Greene, 1999). Additionally, combining medetomidine with opioids can achieve satisfactory sedation while minimizing the neurohormonal and metabolic side effects (Kanda and Hikasa, 2008). Tramadol, which exerts its analgesic effects through central mechanisms by interacting with opioid, adrenergic, and serotonin receptors (Bamigbade and Langford, 1998), has gained

popularity in veterinary medicine due to its classification as an unscheduled drug, its minimal side effect profile, and the convenience of oral administration (Duke-Novakovski et al., 2016).

Various sedatives and anesthetic medications have been documented to result in unfavorable ocular effects, including exposure keratopathy caused by the loss of eyelid reflex, lagophthalmos, compromised stability of the tear film that protects the corneal surface, and diminished basal tear production (Zernii et al., 2016). Dogs (Di pietro et al., 2016) and cats (Ghaffari et al., 2010) have been reported to suffer from transient dry eye. The occurrence of dry eye during the perioperative period may lead to corneal abrasions as a consequence of compromised corneal integrity (Giannetto et al., 2010). Previous studies indicate that administration of alpha-2 adrenergic receptor agonists alone or in combination with opioids decreased tear secretion (TS) in various species (Sanchez et al., 2006; Okur et al., 2022; Wolfran et al., 2022). The objective of this research was to assess the effects of medetomidine and the combination of medetomidine and tramadol, as well as their reversal with atipamezole, on tear secretion in cats.

MATERIALS AND METHODS

All procedures were approved by Atatürk University Local Board of Ethics Committee for Animal Experiments (no: 2022/5) and all owners supplied written informed consent during the examination to be incorporated in the investigation. Before cats were included in the study, the animals underwent thorough examinations to ensure their health. These assessments comprised thorough physical evaluations, a full hematological profile, and visual inspections using both direct and indirect ophthalmoscopic techniques (Aesculap AC635C model by Braun, situated in Tuttlingen, Germany). Additional diagnostic procedures included the measurement of intraocular pressure with a rebound tonometer (specifically the Tonovet brand from Icare, based in Vantaa, Finland), evaluations of tear production with the use of Schirmer's tear test, and the application of a fluorescein dye test. Cats displaying any ocular disease or exhibiting a TS rate of 3 mm/min or lower during the ocular assessment were excluded from the study. The cats were restricted from fasting for 12 hours before beginning the study.

Forty-six healthy cats (22 males and 26 females) presented to the Faculty of Veterinary Medicine Animal Hospital at Atatürk University for diagnostic imaging. All animals were randomly divided in two equal groups: group M [n = 23] and group MT [n = 23]). Cats in group M received intramuscular (IM) medetomidine (80 µg/kg, Domitor; Zoetis, Espoo, Finland) and those in group MT received a combination of IM medetomidine (80 µg/kg) and tramadol (2 mg/kg, Contramal, Abdi Ibrahim, Istanbul) in the same syringe. TS measurements were noted at the following time: T_0 (baseline, immediately before drug administration), T_{15} (+15), T_{30} (+30), T_{45} (+45), and T_{60} (+60). At T_{30}, all cats were administered IM atipamezole (200 µg/kg, Reversal, Provet, Kartal, Istanbul). A 20-minute acclimation period to the environmental conditions and lighting within the study room was provided for each animal before any drug administration. Afterwards, TS measurements were obtained from both the right and left eyes of each cat at T0 (Baseline, Figure 3). The ophthalmologist, who was ignorant of the group allocation, conducted the TS measures from 8:00 to 10:00 a.m. This was done to minimize the impact of individual and daily changes. Bilateral measurements were obtained, and the first eye to undergo testing was chosen at randomly.

The TS reading was obtained by inserting a Schirmer tear test strip (STT-I, AkSchirmer, Devine Meditech, New Delhi, India, lot no: MIPL/A1/54, exp. date: 2026-10) into the ventral conjunctival fornix at the lateral third of the lower eyelid. Making sure the nictitating membrane did not obstruct; the strip was left in touch with the corneal surface for a minute in each eye. The cats were positioned sternally when the measurements were performed.

Statistical analysis

Prior to commencing the investigation, a power analysis was conducted using PS-Power and Sample Size Calculation, Version 3.1.2, developed by Vanderbilt University, TN, USA. The purpose of this analysis was to estimate the minimum sample size necessary for each group. The results showed that a sample size of 23 cats per group would be necessary to detect a difference of more than 3.4 mm/min (± 5 standard deviation (SD)) with a Type I error (α) of 0.05 and a Type II error (Power, β) of 0.80. The aforementioned figure was derived from data acquired in prior investigations conducted on cats (Di Pietro et al., 2016).

The data analysis was carried out using SPSS Version 25.0 software (IBM Company, SPSS, IL, USA). The Shapiro-Wilk test was used to determine that the data had a normal distribution. The left and right eyes were compared using a paired Student's t-test. The differences in the TS by gender were determined using an independent samples t-test. To compare TS values at various time intervals within and across groups, a two-way repeated measures ANOVA was used, followed by *posthoc* Tukey comparison test. Obtained data are reported as the average ± standard deviation, and statistical significance was evaluated by a threshold of P values less than 0.05.

RESULTS

All cats recovered from sedation without complications. The administration of drugs resulted in the observation of vomiting in three and one cats in groups M and MT, respectively. One cat in the MT group was excluded from the study due to obtaining a value of 0 mm/min in T_{15} and T_{30} STT-I readings and artificial tears were administered to the cat.

Both male and female cats had similar TS rates (12.4 ± 3.2 mm/min and 13.1 ± 3.8 mm/min, respectively) with no statistically significant difference (P = 0.15). The mean TS readings at T_0 between the right and left eyes showed no significant both M group (right; 13.3 ± 3.3 mm/min, left; 13.4 ± 3.6 mm/min, P = 0.949) and MT group (right; 13.2 ± 4.8 mm/min, left; 11.7 ± 4.7 mm/min, P = 0.490, Figure1, Table 1). Therefore, the mean TS readings obtained from both eyes were employed as a mean value for each cat at all-time points.

Table 1. Right and left eye tear secretion (TS mm/min) measurements using Schirmer tear test (STT1) of intramuscular 80 µg/kg medetomidine (Group M) and 80 µg/kg medetomidine + 2 mg/kg tramadol (Group MT) in cats. Data are presented as mean ± standard deviation.

Groups	Eye	TS	P value
M	Right	13.3 ± 3.3	0.949
	Left	13.4 ± 3.6	
MT	Right	13.2 ± 4.8	0.490
	Left	11.7 ± 4.7	

Both the M and MT groups showed a substantial reduction in TS at T15, T30, and T45 compared to T0 ($P < 0.05$, Figure 1). The M group had a TS decrease of 44.8% at T30, whereas the MT group exhibited a higher drop of 69% at the same time point. Following atipamezole administration at T_{30}, the TS progressively increased until T_{60} in both groups. However, no significant difference was found between T_{60} and T_0 in both groups (Figure 2). Although, there is not statistically significant difference between T_{60} and T_0, the TS readings did not reach the baseline values in both groups at the end of study (T_{60}). The lowest TS value recorded throughout the study was 2.7 and 4.9 mm/min in MT and M groups, respectively.

At time T_0, there was no statistically significant differences observed in the mean TS readings between the M (13.4 ± 2.9 mm/min) and MT (12.6 ± 4.3 mm/min) groups ($P = 0.51$). A significant difference between groups was observed in TS readings at T_{15} and T_{30} ($P = 0.03$). Following atipamezole administration in both groups, no significant difference was observed at T_{45} and T_{60} between groups ($P = 0.89$ and $P = 0.93$, respectively, Table 2). The effects on TS of the group-time interactions were statistically significant ($P = 0.01$).

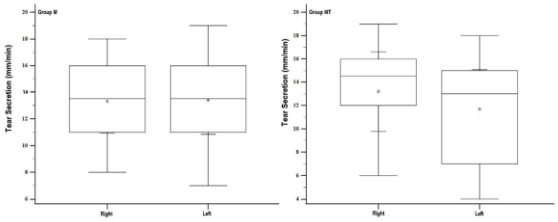

Figure 1. Comparison of mean right and left eye tear secretion (TS, mean ± SD) results (mm/min) in 80 µg/kg medetomidine (M group) and 80 µg/kg medetomidine + 2 mg/kg tramadol (MT group) in cats.

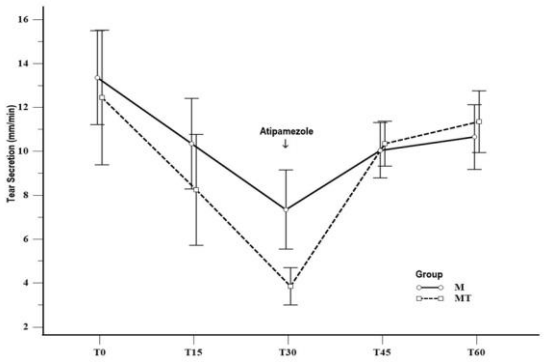

Figure 2. Mean ± SD tear secretion (TS, mm/min) following administration of 80 µg/kg medetomidine (M group) and 80 µg/kg medetomidine + 2 mg/kg tramadol (MT group) at various time points in cats.

Figure 3. Tear secretion measurements in both the right and left eye in a cat

Table 2. Effect of 80 µg/kg medetomidine (Group M) and 80 µg/kg medetomidine + 2 mg/kg tramadol (Group MT) administration on tear secretion (TS, mm/min) measurement using Schirmer tear test (STT1) before (T_0) and every 15 minutes until 60 min (T_{60}).

Group	Baseline (T_0)	T_{15}	T_{30}	T_{45}	T_{60}
M	13.4 ± 2.9	10.4 ± 2.9*†	7.4 ± 2.5*†	10.1 ± 1.8*	11.7 ± 2.0
MT	12.6 ± 4.3	8.6 ± 3.6*†	3.9 ± 1.2*†	10.4 ± 1.4*	11.4 ± 1.9

*Significantly different from baseline within the treatment ($p < 0.05$) †Significantly different between treatments ($p < 0.05$). Data expressed mean ± standard deviation.

DISCUSSION AND CONCLUSION

The current investigation demonstrated that IM administration of medetomidine and medetomidine-tramadol combination progressively reduced TS, as measured by STT-I, in cats until administration of atipamezole. Following the administration of atipamezole, there was a gradual increase in TS observed in both groups. At the end of study, the TS values did not reach the baseline values in either of the groups, but there is no significant difference was found between baseline and end of study.

One of the most common adverse effects of α2-agonists in cats is vomiting. A previous study reported a vomiting rate of 7% in cats following administration of α2-agonists (Granholm et al., 2006). Similarly, in our study, the rate of vomiting in cats administered medetomidine was 9%. The low incidence of reported vomiting in this study may be attributed to the implementation of appropriate fasting periods.

Multiple investigations have shown that TS in different animal species may be influenced by sedatives or a combination of sedatives and opioids (Ghaffari et al., 2010; Giannetto et al., 2021; Okur et al., 2022; Cinar et al., 2024). Multiple variables influence the alterations in TS induced by sedatives and opioids. These aspects include the impact on the central nervous system, the constriction of tear glands leading to reduced tear production, metabolic changes, and the alleviation of pain due to the analgesic qualities of opioid medications (Dodam et al., 1998). Furthermore, another potential cause for the

reduced level of tear stability (TS) might be attributed to the sedative medicine, which likely slowed down the frequency of blinking and heightened the pace of tear evaporation (Leonardi et al., 2019). Our investigation demonstrated that the injection of medetomidine, either alone or in combination with tramadol, effectively decreased TS in cats, aligning with previous research results. Previous studies have shown similar findings in dogs that were administered medetomidine either alone or in conjunction with butorphanol (Sanchez et al., 2006).

The present investigation suggested that IM administering a combination of medetomidine and tramadol resulted in more pronounced reduction in TS compared to that administering by medetomidine alone. Moreover, cat in the MT group had the lowest TS value. Our findings are in good agreement with a previous study, conducted on horses, which suggested that administering detomidine with butorphanol intravenously results in a more profound and longer reduction in TS compared to detomidine alone (Leonardi et al., 2020). These results might be explained in part by the fact that medetomidine and tramadol may have additive and/or synergistic effects in lowering cats' TS, enhancing analgesia, and influencing hemodynamic changes and neurophysiological mechanisms (Bianchi et al., 2015; Leonardi et al., 2019). Additionally, the reduced quantifiable TS resulting from the combination of medetomidine and tramadol may be a consequence of opioid-induced changes in lacrimal gland metabolism (Mourney et al., 2011). However, further research is required to elucidate the impact of IM tramadol by itself on TS.

Atipamezole effectively counteracted the decrease in TS in all treatment groups. Our hypothesis is that the reduction in TS resulted in medetomidine is affiliated with the sedative or hemodynamic effects of the medication. The α2-antagonist restored TS to almost its initial levels, maybe by counteracting the effects of the α2-agonist. Additional research conducted by Sanchez et al. (2006) on dogs and Wolfran et al. (2022) on cats similarly found that the administration of atipamezol effectively counteracted the decrease in TS caused by α2-antagonists.

Readings of STT I in clinically healthy cats have been observed to range from 3 to 32 mm/min (Maggs et al., 2013). Therefore, cats having STT I value of 3 mm/min or below were excluded from our study. Previous studies have reported diurnal variation of TS in human (Masmali et al., 2015), dogs (Hartley et al., 2006), and horses (Piccione et al., 2008). Hence, TS measurements were conducted on all cats in our research between 08:00 and 10:00 a.m. to avoid diurnal variation.

The current study indicated that medetomidine alone or in combination with tramadol caused a significant reduction in the TS shortly after IM administration in cats. In cats, clinicians should measure STT before using medetomidine or the combination of medetomidine and tramadol as a sedative to accurately evaluate the results. Furthermore, it is crucial to utilize a sterile eye ointment or tear replacement as a corneal protectant after administering drugs to cats.

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Conflict of Interest

The authors declare that they have no competing interests.

Authorship contributions

Concept: E.T.C, S.O., Design: E.T.C, S.O., Data Collection or Processing: E.T.C, S.O., Analysis or Interpretation: S.O., Literature Search: E.T.C, S.O., Writing: S.O.

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