An anesthetic drug in combination with a sedative is commonly used in feline practice to induce a state that will enable clinicians to perform routine invasive procedures, radiographic examinations, castration, and ovariohysterectomy or to provide dental care. Sometimes it is necessary to use anesthesia characterized by a rapid onset after administration, adequate duration of action, appropriate analgesic effects, and rapid return to function, particularly when feral cats are undergoing castration or ovariohysterectomy during programs to reduce populations, such as trap-neuter-return programs. Adverse effects of medetomidine include low oxygen saturation as measured by use of pulse oximetry and transient hypoxemia. Use of injectable anesthetic drugs can influence ocular tear production in various animal species, such as dogs, cats, and horses, by causing a reduction of the aqueous component of the tear film. In 1 study, tear production in cats decreased 30 minutes after preanesthetic administration of atropine sulfate and induction of anesthesia by use of ketamine hydrochloride in combination with acetylpromazine and ketamine hydrochloride (5 mg/kg), and an experimental group (30) anesthetized with the medetomidine-ketamine combination and reversal by administration of atipamezole. Tear production of both eyes of each cat was measured by use of the STT I before the beginning of anesthesia, and 15 minutes after administration of atipamezole. Tear production nearly to preanesthetic values within 15 minutes after reversal with atipamezole, whereas the STT I values for the control group were still low at that point.

**RESULTS**

Anesthesia with a medetomidine-ketamine combination of cats with no ophthalmic disease caused a significant decrease in tear production. The STT I values returned nearly to preanesthetic values within 15 minutes after reversal with atipamezole, whereas the STT I values for the control group were still low at that point.

**CONCLUSIONS AND CLINICAL RELEVANCE**

Results indicated that a tear substitute should be administered to eyes of cats anesthetized with a medetomidine-ketamine combination from the time of anesthetic administration until at least 15 minutes after administration of atipamezole. (Am J Vet Res 2016;77:310–314)
tion with ketamine on STT I results for cats. Thus, the objective of the study reported here was to investigate the effects of a medetomidine-ketamine combination on tear production in clinically normal cats before and during anesthesia and after reversal of medetomidine with atipamezole.

**Materials and Methods**

**Animals**

Forty client-owned crossbreed domestic shorthair cats (23 males and 17 females) were used in the study. Cats were between 6 and 24 months of age and were anesthetized for elective castration or ovariohysterectomy. A complete physical examination, CBC, and ophthalmic examination, including indirect ophthalmoscopy, slit-lamp biomicroscopy, STT I, and fluorescein staining, were performed on both eyes of all cats. Cats that were of domestic shorthair breed, had no abnormalities detected during physical and ophthalmic examinations, and were not receiving any ocular medications were eligible for participation in the study.

Preanesthetic testing by use of the STT I was performed by inserting a standard sterile strip within the ventral conjunctival fornix for 1 minute. All strips were from the same batch. The strip was placed in the lower eyelid at the junction of the middle and temporal thirds. Tearing rate was reported as the length of strip (in millimeters) that became wet in 60 seconds. Cats with tear measurements < 10 mm/min were not included in the study.

All treatments, housing, and animal care were in accordance with EU Directive 2010/63/EU for animal experiments. All owners provided consent for use of their animals in the study.

**Procedures**

All cats received a combination of medetomidine hydrochloride (80 µg/kg) and ketamine hydrochloride (5 mg/kg), which was mixed in a 1-mL syringe and injected IM into the paralumbar muscles. The amount of time each cat was anesthetized differed depending on the surgical procedure; however, anesthetic time did not exceed 45 minutes for any cat. Cats were allocated into 2 groups. The control group consisted of 10 cats (5 males and 5 females); these cats were anesthetized with the medetomidine-ketamine combination and did not receive a reversal agent. The experimental group consisted of 30 cats (18 males and 12 females); these cats were anesthetized with the medetomidine-ketamine combination, and the effects of medetomidine were reversed by IM administration of atipamezole hydrochloride (equal to half the amount of medetomidine). Atipamezole was injected in males 30 minutes after the beginning of anesthesia, whereas it was injected in females between 30 and 45 minutes after the beginning of anesthesia.

**Data collection**

The same investigator (SD) performed all clinical examinations and obtained all STT I measurements. The STT I data obtained prior to anesthesia in the unanesthetized cats were considered baseline values. The STT I values were obtained for both eyes of all cats 15 minutes after administration of anesthetics and 15 minutes after administration of atipamezole. All experimental procedures were performed between 2:00 PM and 4:00 PM.

**Statistical analysis**

Statistical analysis was performed by use of a general linear modeling program. For the experimental group, the STT I result was defined as the dependent variable, and time (before anesthesia [T0], 15 minutes after beginning of anesthesia [T15], and 15 minutes after administration of atipamezole [Tlast]), age, and sex were considered independent variables. This group was categorized into 2 subgroups consisting of 18 young (6 to 11 months old) and 12 adult (12 to 24 months old) cats and into 2 other subgroups consisting of 18 male and 12 female cats.

Effects of reversal of medetomidine by administration of atipamezole were evaluated by comparing STT I results between the experimental and control groups. The Bonferroni multiple comparison test was used for post hoc comparisons. Results were considered significant at $P < 0.05$.

**Results**

Mean values for tear production of the cats were determined. There were no effects of age or sex on mean STT I values at any time (T0, T15, and Tlast) for the experimental group (Figure 1). Mean ± SD STT I values were > 15 mm/min before anesthesia (16.66 ± 4.99 mm/min for young cats and 17.75 ± 6.94 mm/min for adult cats), decreased to < 15 mm/min dur-

![Figure 1](image-url)
Evaluation of the effects of atipamezole reversal on STT I values revealed a significant difference between the experimental and control groups. Values for both groups differed significantly (P < 0.001) over time. In addition, the STT I measurements obtained at Tlast were significantly (P < 0.001) higher for the experimental group than for the control group (Figure 2).

Discussion

Aqueous tear production of cats is routinely measured with STT strips. The STT I measures both basal lacrimal production and reflex tearing that is induced by contact of the paper strip with the ocular surface. To determine basal values for tear formation, the STT II is performed after administration of topical anesthetic. The STT II is performed after administration of topical anesthetic and drying of the lower conjunctival fornix with a cotton swab. Results of the STT II for clinically normal cats reportedly are approximately 80% of the STT I values.6

Because a decreased rate of tear production may cause ocular pathology, we evaluated the effect of a commonly used anesthetic protocol on tear production in cats by use of the STT I and a procedure reported in similar studies.5–7 Basal mean STT I values of cats measured before the administration of anesthetic drugs in the present study did not differ from the mean reported for felids (16.9 mm/min).6

To our knowledge, there have been no reports published previously regarding the effects of medetomidine in combination with ketamine on STT results in cats. Analysis of the results for the present study indicated that IM injection of a drug combination of medetomidine and ketamine to clinically normal cats caused a rapid significant decrease in STT I values from baseline values. The STT I values nearly returned to preanesthetic values within 15 minutes after medetomidine reversal with atipamezole, but they remained low when atipamezole was not administered.

Data obtained in the present study on the effects of medetomidine on STT I values in cats are in accordance with results for dogs,5 with a significant decrease of tear production after administration of medetomidine alone or in combination with sedatives. The study of cats reported here also indicated results similar to those reported for dogs with regard to the return to baseline STT values at 15 minutes after atipamezole administration.

The exact mode of action of sedatives for decreasing lacrimation in dogs and cats is unclear. Inhibitory effects of acepromazine and xylazine on tear production as measured with the STT I were evaluated for clinically normal cats in another study,4 and the effects of sedative and opioid combinations on tear production have been evaluated for dogs.7 It has been reported1 that xylazine, an α2-adrenergic agonist similar to medetomidine, decreases heart rate in cats by enhancing vagal tone and baroreceptor reflexes.

One possible mechanism for the reduced tear production may be changes of some ocular variables (central eye position, lack of a blink reflex, decrease in corneal sensitivity, and impairment of tearing reflex) during anesthesia (as induced by administration of the medetomidine-ketamine combination). In 1 study,7 it was suggested that STT I values were lower when dogs were under the effects of sedative-opioid combinations, possibly because of one or more of the following mechanisms: central effects of these drugs on autonomic regulation of tear production, effects of antinociception, vasoconstriction at the tear gland, and altered metabolism at the tear gland cellular level.

Furthermore, it is important to mention that control by the CNS is the primary factor regulating tear secretion.8 The lacrimal gland is innervated by the lacrimal nerve, which is a branch of the trigeminal nerve. The latter is mainly a sensory nerve, but it also conveys parasympathetic (cholinergic) and probably sympathetic (adrenergic) fibers to the lacrimal gland. Both nerve fiber types are distributed around acini and blood vessels, which suggests a role of these autonomic fibers in the control of lacrimal secretion.8,10 It has also been found in cats that the secretory fibers conveyed by the lacrimal nerve to the lacrimal gland are cholinergic; therefore, anticholinergic drugs such as atropine and tropicamide can cause hypolacrimation.5,11 In clinically

Figure 2—Mean STT I values obtained at T0, T15, and Tlast for 30 cats anesthetized by IM administration of a medetomidine-ketamine combination and reversed by administration of atipamezole (experimental group [circles]) and 10 cats anesthetized by IM administration of a medetomidine-ketamine combination and not reversed by administration of atipamezole (control group [squares]). *Within a time point, value differs significantly (P < 0.001) from the value for the control group. a,bWithin a group, values with different letters differ significantly (P < 0.001). See Figure 1 for remainder of key.
normal cats, a single dose of 1% tropicamide in 1 eye causes significant reductions in tear production of both eyes at 1 hour after tropicamide application, and the tear production returns to baseline values by 4 hours after tropicamide application; this effect is apparently related to systemic adsorption of this anticholinergic drug.\textsuperscript{12}

A second mechanism implicated in causing a reduction of tear secretion could be related to the main action of opioid drugs (antinociception) that causes a decrease of reflex tear production.\textsuperscript{7} An alternative explanation for the decrease in the rate of tear production is based on \(\alpha_2\)-adrenoreceptor-mediated effects of medetomidine in dogs and cats, which determine sedation and analgesia as well as bradycardia, respiratory depression, muscle relaxation, decreased intestinal motility, increased urine volume, and decreased intraocular pressure.\textsuperscript{6,13}

Cardiovascular and respiratory effects represent baroreceptor responses to arterial hypertension attributable to peripheral vasoconstriction secondary to the activation of \(\alpha_2\)-adrenoreceptors located on the smooth muscle fibers of blood vessels. The vasoconstriction causes a decrease in tear production by diminishing the blood flow to tear-producing glands. A final hypothesized mechanism suggests that sedatives and opioids (eg, xylazine and butorphanol) can exert their effects at the cellular level in tear-producing cells by directly altering the cellular responses to stimuli.\textsuperscript{7}

In the present study, the inhibitory effect on tear production (as measured by use of the STT I) in clinically normal cats attributable to the sedative-anesthetic combination was evident by 15 minutes after the IM injection. The decrease of tear production was mainly caused by medetomidine. After reversal with atipamezole, medetomidine no longer exerted its effects on the lacrimal gland; therefore, the STT I values returned to within the physiologic range. Conversely, in the control cats that did not receive atipamezole, the STT I values still remained significantly low.

The role of ketamine on reduction of tear production in the cats of the present study cannot be confirmed because we did not include a separate group of cats anesthetized with ketamine alone. Ketamine is not routinely used as the sole anesthetic agent for surgical procedures such as neutering of cats.

Comparison between the subgroups (young vs adult and males vs females) revealed that these variables had no effect on STT I values. Age and sex of the cats did not influence the response of lacrimal glands to anesthesia.

In the present study, the duration of anesthesia for each cat was variable, depending on the surgical procedure, with no surgery requiring > 45 minutes. Castration generally required less time than did ovariohysterectomy, so reversal of the medetomidine was performed at different time points (30 minutes for males and between 30 and 45 minutes for females). However, this difference did not affect the postanesthetic results, as indicated by the increase of STT I values to > 15 mm/min for all cats after administration of atipamezole. Furthermore, comparison of the STT I values of males versus females revealed no significant differences at any time.

Although the combination of medetomidine and ketamine is a commonly used and adequate injectable anesthetic regimen for use in surgery in cats,\textsuperscript{1} this drug combination reduces aqueous tear production as determined by use of the STT I. We believe that regardless of age and sex, cats undergoing anesthesia with the medetomidine-ketamine combination should be administered sterile ocular lubricant or tear replacement solution as a corneal protectant during the anesthetic period. It is extremely important to reapply the topical tear supplement during and after anesthesia and to monitor corneal hydration for at least 15 minutes after reversal of medetomidine with atipamezole to prevent a prolonged period of a dry ocular surface, which could predispose a cat to the onset of ulcerative keratitis.

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\section*{Footnotes}

a. Dina Strip Schirmer-Plus, GECIS sarl, Neung sur Beuvron, France.

b. Domitor, Pfizer Animal Health, Milano, Italy.

c. Ketavet 100, Intervet Production Srl, Aprilia-Latina, Italy.

d. Antisedan, Pfizer Animal Health, Milano, Italy.


\section*{References}


10. Powell CC, Martin CL. Distribution of cholinergic and adren-