Effects of acepromazine maleate or morphine on tear production before, during, and after sevoflurane anesthesia in dogs

Meredith C. Mouney, DVM; Peter J. Accola, DVM, MS; Jeannette Cremer, DVM; Molly K. Shepard, DVM; Carolina Rodriguez Guarin, DVM; Erik H. Hofmeister, DVM, MA

Objective—To investigate the effects of acepromazine maleate and morphine on aqueous tear production before, during, and after sevoflurane anesthesia in dogs.

Animals—6 mixed-breed dogs.

Procedures—In a Latin square study design, dogs underwent IM administration of morphine (1 mg/kg), acepromazine (0.05 mg/kg), or saline (0.9% NaCl) solution (0.05 mL/kg), followed by induction and maintenance of anesthesia with sevoflurane for 30 minutes. The protocol was repeated until all dogs had received all treatments, with a minimum of 7 days between anesthetic episodes. Aqueous tear production was measured via Schirmer tear test I before treatment (baseline); before anesthetic induction; 5, 10, 20, and 30 minutes after anesthetic induction; immediately once dogs recovered from anesthesia; and 2 and 10 hours after recovery.

Results—Aqueous tear production for all treatments was significantly lower 10, 20, and 30 minutes (but not 5 minutes) after anesthetic induction than at baseline, before anesthetic induction, at recovery, and 2 and 10 hours after recovery. Aqueous tear production was significantly higher after saline solution administration than after morphine administration at the preinduction measurement point and 2 hours after recovery. No other differences were detected among the 3 treatments.

Conclusions and Clinical Relevance—Aqueous tear production after anesthesia did not differ significantly from baseline values after any treatment following 30 minutes of sevoflurane anesthesia, suggesting premedication with morphine or acepromazine does not contribute to a decrease in lacrimation in these circumstances. (*Am J Vet Res* 2011;72:1427–1430)

The health of the ocular surface depends, in part, on preocular tear film.[1] This tear film confers a smooth optical surface for light refraction, provides lubrication, removes debris, prevents microbial colonization of the eye, and supplies nutrients to the avascular cornea.

Clinical estimation of tear production in dogs is routinely performed with the STT, and STT I is used to estimate basal and reflex tearing function.[2] Anesthetics and preanesthetic agents can cause a reduction in tear production.[3–7] The reduction caused by anesthesia can have clinical consequences, including drying of the cornea and irritation from inhalation anesthetic vapor.[8] Corneal drying and exposure during and after an anesthetic event can lead to corneal pathological changes such as ulceration, which, depending on its progression, may substantially affect vision.

Abbreviation

STT Schirmer tear test

Premedications are used in most anesthetic protocols to provide sedation and analgesia, decrease the amount of anesthetic induction agent needed, and decrease the minimum alveolar concentration of inhalation anesthetics. Many premedication combinations include an opioid plus a sedative such as acepromazine maleate, diazepam, or medetomidine HCl. Numerous sedative opioid options, including medetomidine alone, medetomidine and butorphanol, acepromazine and oxymorphone, diazepam and butorphanol, xylazine HCl and butorphanol, and butorphanol alone, reportedly cause transiently dry eyes after administration.[4,5] However, the effects of treatment with acepromazine or morphine on postanesthetic tear production in dogs have not been reported, nor has the effect of acepromazine treatment alone. The purpose of the study reported here was to investigate the effects of acepromazine maleate and morphine, used as premedications, on tear production before, during, and after anesthesia in dogs. The hypothesis was that acepromazine and morphine

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From the Departments of Small Animal Medicine and Surgery (Mouney, Accola, Shepard, Rodriguez Guarin, Hofmeister) and Large Animal Medicine (Cremer), College of Veterinary Medicine, University of Georgia, Athens, GA 30602. Dr. Mouney's present address is Department of Veterinary Clinical Science, School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907. Dr. Accola's present address is Wisconsin Veterinary Referral Center, 360 Bluemound Rd, Waukesha, WI 53188.
The sevoflurane used in this project was donated by Abbott Laboratories.
Address correspondence to Dr. Hofmeister (kaastel@uga.edu).

would cause a decrease in intra-anesthetic tear production, which would resolve within 2 hours after anesthetic recovery.

Materials and Methods

Animals—Six random-source mixed-breed dogs with no known underlying systemic disease were used in the study. All dogs underwent a complete ophthalmic examination by an experienced veterinarian (PJA) prior to each anesthetic episode, including slit-lamp biomicroscopy,[a] STT,[b] fluorescein stain[c] of the cornea, measurement of intraocular pressure with an applanation tonometer,[d] and indirect ophthalmoscopy with a 2.2 panretinal indirect lens.[e] Sample size analysis, based on a previous study[9] in which similar methods were used, revealed that 6 dogs would be the minimum number needed to achieve an α of 0.05 and β of 0.80 and to detect a difference of 5 mm in tear production at 2 hours after anesthesia. The study protocol was approved by the University of Georgia Animal Care and Use Committee, with husbandry provided according to established institutional guidelines.

Experimental procedure—A Latin square design was used, with each dog undergoing each of 3 treatments in a separate trial: morphine[f] (1 mg/kg, IM), acepromazine maleate[g] (0.05 mg/kg, IM), or saline (0.9% NaCl) solution (0.05 mL/kg, IM) prior to an anesthetic episode. Each trial took place between 7 AM and 11 PM, with a minimum of 7 days between each. Body condition score (9-point scale),[10] body weight, and baseline aqueous tear production (with dogs gently restrained for performance of an STT I) were measured for each dog immediately prior to each anesthetic event by a single observer who was unaware of which treatment dogs had received.

After dogs received the assigned treatment, they were allowed to rest for 30 minutes, after which an IV catheter was placed in a cephalic vein. A preinduction STT was performed, then anesthesia was induced via face mask with sevoflurane[h] at the maximum vaporizer setting for the agent (8%) at an oxygen flow rate of 3 L/min. Each dog was subsequently orotracheally intubated and positioned in right lateral recumbency. End-tidal sevoflurane concentrations were measured with a calibrated gas analyzer[i] by means of a sidestream sampling T-piece located between the endotracheal tube and the Y-piece of the anesthesia circuit. Esophageal temperature was measured continuously via a probe placed in the thoracic esophagus and was maintained between 36.9° and 37.8°C by use of a blanket placed over the patient and warmed with a forced-air warming unit.[j]

Within 10 minutes after anesthetic induction, the vaporizer was set to achieve an end-tidal sevoflurane concentration of 3.2%, which represents 1.5 times the minimum alveolar concentration value for sevoflurane.[11] After the target concentration was achieved, the oxygen flow was decreased to 2 L/min for the remainder of anesthesia, each episode of which lasted 30 minutes. Dogs were allowed to breath spontaneously throughout each anesthetic episode.

Measurement of aqueous tear production—Prior to performance of the STT I, the inferior cul-de-sac of each eye was gently swabbed with a cotton-tipped applicator to remove accumulated tears and mucus. One investigator (JC), who was blinded to treatment received, performed an STT I at 5, 10, 20, and 30 minutes after anesthetic induction. Aqueous tear production was measured in millimeters of wetting per minute by placing the tear test strip in the ventral conjunctival fornix approximately a third of the distance from the lateral to medial canthi. Both eyes were irrigated immediately after the 10-, 20-, and 30-minute measurements with sterile isotonic buffered water.[k] No effort was made to close the dogs' eyes during the experiment, and no other interventions were performed during anesthesia.

The STT I was again performed once dogs had recovered from anesthesia and were standing (recovery). Thereafter, sterile ophthalmic ointment[l] was applied to both eyes to protect the ocular surface. The test was later performed 2 and 10 hours after recovery.

Statistical analysis—Normality of data distribution was determined by use of the Shapiro-Wilk test. Differences among groups in body condition score, body weight, and baseline tear production over each week were determined via repeated-measures ANOVA. Tear production data were analyzed with an ANOVA with repeated measures for changes within a treatment

Table 1—Mean ± SD (95% confidence interval) aqueous tear production as determined via STT I in 6 mixed-breed dogs treated with morphine (1 mg/kg, IM), acepromazine maleate (0.05 mg/kg, IM), or saline (0.9% NaCl) solution (0.05 mL/kg, IM) at various points before treatment (baseline) and before, during, and after (recovery) from sevoflurane anesthesia.

Time point	Saline solution	Acepromazine	Morphine
Baseline	18 ± 4 (15 to 20)	20 ± 3 (18 to 22)	17 ± 4 (14 to 20)
Before anesthetic induction*	23 ± 6 (20 to 27)	20 ± 4 (18 to 23)	18 ± 3 (16 to 20)
5 min	6 ± 4 (3 to 9)	6 ± 4 (3 to 8)	3 ± 6 (–1 to 7)
10 min†	1 ± 2 (–1 to 2)	1 ± 2 (0 to 3)	1 ± 3 (–1 to 3)
20 min†	1 ± 2 (0 to 3)	2 ± 3 (0 to 3)	1 ± 2 (–1 to 2)
30 min†	1 ± 2 (0 to 2)	2 ± 3 (0 to 4)	0 ± 0 (0)
Recovery	25 ± 3 (23 to 26)	20 ± 5 (17 to 23)	21 ± 6 (17 to 25)
2 h*	26 ± 2 (25 to 28)	23 ± 3.5 (20 to 25)	21 ± 3 (19 to 23)
10 h	24 ± 4 (22 to 26)	23 ± 3 (21 to 24)	21 ± 3 (19 to 23)

*Values differ significantly between morphine and saline solution treatments. †Values in this row differ significantly ($P < 0.05$) from respective values at baseline, before anesthetic induction, at recovery, and 2 and 10 hours after recovery.

over time and an ANOVA with a Tukey test for post hoc testing for comparisons among treatments. A paired *t* test was performed to compare tear production in the left versus right eyes. Values of $P < 0.05$ were considered significant. Results of STT I and body weight measurement at the various measurement points are reported as mean ± SD.

Results

Animals—Ophthalmologic examinations performed on the 6 dogs before the experiment began revealed no abnormal findings. Body condition score did not differ significantly ($P = 0.25$) throughout the 3-week, 3-trial study period. However, dogs weighed significantly ($P < 0.01$) less each week (mean ± SD body weight was 22.6 ± 2.5 kg, 22 ± 2.5 kg, and 21.6 ± 3.3 kg for weeks 1, 2, and 3, respectively). There was no significant ($P = 0.62$) difference in STT values between right and left eyes throughout weeks 1, 2, and 3; therefore, data were pooled.

Aqueous tear production—Tear production before treatment was administered (baseline) did not differ significantly ($P = 0.92$) among the 3 treatment trials (**Table 1**). Tear production was significantly ($P < 0.01$) lower for all treatments at 10, 20, and 30 minutes but not at 5 minutes after anesthetic induction, compared with respective values at baseline, before anesthetic induction, at recovery, and 2 and 10 hours after recovery. At the preinduction measurement point and 2 hours after recovery, tear production was significantly ($P < 0.02$) higher after treatment with saline solution than after treatment with morphine. No other significant differences in tear production were detected among the 3 treatments.

Discussion

In clinical practice, a healthy mean ± SD rate of aqueous tear production as measured via STT I is considered 19.8 ± 5.3 mm of wetting/min or 21 ± 4.2 mm of wetting/min.[3] In the study reported here, tear production did not decrease to less than this rate when dogs were treated with saline solution, morphine, or acepromazine maleate and measured before induction of sevoflurane anesthesia, at recovery from anesthesia, and 2 and 10 hours after recovery.

Morphine is a commonly used premedication agent because of its effectiveness and low cost. The exact mechanism of action of morphine on lacrimation in dogs is unknown. Four mechanisms have been proposed to explain the decrease in aqueous tear production as measured via STT I when dogs are treated with certain sedative opioid combinations.[5] These mechanisms include central drug effects on the autonomic regulation of tear production, effective antinociception, constriction of blood vessels supplying the tear-producing glands, and altered gland cellular metabolism.[5] In the present study, treatment with saline solution resulted in different tear production rates than those of morphine before anesthetic induction and 2 hours after recovery. This finding may have been attributable to one or more of the previously proposed mechanisms[5]; however, it was beyond the scope of our study to explore the potential mechanism. The lack of a difference in tear production between morphine and saline solution treatments during anesthetic recovery might be explained by the sympathetic effects during recovery overriding other influences on tear production.

Acepromazine is a neuroleptic agent, the primary mechanism of action of which is postsynaptic inhibition of central dopamine receptors.[12] It can cause depression of respiratory and heart rates and a decrease in blood pressure and body temperature.[12] At no point did acepromazine treatment significantly alter tear production relative to morphine or saline solution treatment. Because acepromazine does not produce analgesia or vasoconstriction, it would not have influenced lacrimation through those mechanisms. In another study,[4] treatment of dogs with the combination of acepromazine and oxymorphone resulted in a significant decrease in tear production; however, acepromazine treatment alone was not evaluated. Therefore, it is possible that the reported decrease was attributable to the effects of the oxymorphone and not acepromazine. In cats, sedation with acepromazine or xylazine reportedly leads to a decrease in tear production.[6] This acepromazine effect, which was not detected in the present study, may be specific to cats or may have resulted from a higher dose of acepromazine (0.2 mg/kg) than was used in our study (0.05 mg/kg).

Tear production in dogs can be classified as basal or reflexive. Tears that are continually being produced and transported onto the ocular surface are considered basal tears.[5] Autonomic depression accounts for decreases in reflex tear production in anesthetized dogs.[8] In the present study, all 3 treatments resulted in a severe decrease in tear production at 10, 20, and 30 minutes after anesthetic induction. This is similar to findings during isoflurane and desflurane anesthesia.[9] The decrease in intra-anesthetic lacrimation observed in the present study may be attributable to vagolytic or sympathomimetic effects of the inhalation anesthetic.[7,13,14] Tear production rates as measured via STT I were significantly lower than baseline values for up to 24 hours after anesthetic recovery in a different study,[3] suggesting that anesthesia has a prolonged effect on postanesthetic lacrimation. The dogs in that study that underwent a longer anesthetic episode and had anticholinergics added to their anesthetic protocols had significantly lower aqueous tear production than did the dogs that underwent an anesthetic episode < 2 hours and those that did not receive anticholinergics. No causal relationship could be established because of the various surgical procedures used, the variable use of anticholinergics, and the type of study design. In the present study, aqueous tear production did not differ significantly from baseline for any of the 3 treatments following anesthesia, suggesting that morphine and acepromazine did not cause a decrease in lacrimation after anesthesia. The effect of these drugs on tear production may be dose dependent, but because only 1 dose of each drug was evaluated, such a relationship remains unknown. Because aqueous tear production decreased during anesthesia, as has been observed in other studies,[3–7] we recommend that ocular lubricants be used before, periodically

throughout, and immediately following an anesthetic episode.

a. SL-15, Kowa Optimed Inc, Torrance, Calif.
b. 35 × 5-mm strips, Schering-Plough Animal Health Corp, Union, NJ.
c. Fluor-I-Strip-A.T., Bausch & Lomb Pharmaceuticals Inc, Tampa, Fla.
d. Reichert Tono-Pen, Reichert Inc, Depew, NY.
e. Pan Retinal 2.2, Volk Optical Inc, Mentor, Ohio.
f. Baxter Healthcare Corp, Deerfield, Ill.
g. PromAce, Aveco, Fort Dodge, Iowa.
h. Ultane, Abbott Laboratories, North Chicago, Ill.
i. Ohmeda 5250 RGM, BOC Health Care Co Division, Louisville, Colo.
j. Bair Hugger, Arizant Healthcare Inc, Eden Prairie, Minn.
k. Eye Wash, Hi-Tech Pharmacal Co Inc, Amityville, NY.
l. Puralube, E. Fougera & Co, Melville, NY.

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