Effect of duration and type of anesthetic on tear production in dogs

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Objective—To determine effects of duration and type of anesthetic on tear production in dogs.

Animals—8 female Beagles.

Procedures—Each dog was randomly allocated into 1 of 4 groups according to a Latin square design to receive anesthesia as follows: 1 hour with isoflurane, 1 hour with desflurane, 4 hours with isoflurane, and 4 hours with desflurane. Each dog was anesthetized with the selected inhalant 4 times during a 4-week period, with at least 5 days separating anesthetic episodes. Aqueous tear production was measured via the Schirmer I tear test at baseline and 10 minutes, 30 minutes, and 1 hour after induction of anesthesia as well as 2, 3, and 4 hours after induction for the 4-hour groups. Tear production was also measured after the dogs were standing after recovery from anesthesia and 2, 10, and 22 hours after recovery from anesthesia.

Results—Aqueous tear production was significantly reduced in dogs during anesthesia and returned to baseline values immediately after recovery and until 10 hours after anesthesia in all treatment groups. Inhalant type and duration had no significant effect. Neither lateral recumbency nor left versus right eyes had a significant effect.

Conclusions and Clinical Relevance—Results suggested that inhalant anesthetics did not reduce tear production after anesthesia and that longer-duration anesthesia did not cause decreased tear production, compared with shorter-duration anesthesia. (Am J Vet Res 2011;72:608–612)

The lacrimal glands of the canine orbit and nictitating membrane produce the aqueous portion of the trilaminar preocular tear film, which is integral to protection and nutrition of the cornea.1–3 Lacrimal secretions additionally contribute to ocular surface immunity by delivery of secretory immunoglobulins (mostly IgA), albumin, lipocalin, interleukins, and antibacterial compounds such as lysozyme and lactoferrin.3–5 Aqueous tears also provide mechanical protection to the cornea as a lubricant that flushes debris and bacteria from the corneal surface.3

The cornea is particularly vulnerable to injury during episodes of general anesthesia, when the palpebral reflex, corneal reflex, and purposeful movement cannot protect the eye from drying, corneal abrasions, or other direct corneal injury.6,7 Results of studies in humans suggest both components of tear production (ie, reflex and basal components) are decreased during general anesthesia. Cross and Krupin8 determined that basal tear production is significantly reduced in human patients during general anesthesia and suggested that reflex tear production is concurrently decreased because of autonomic depression. As described by Snow et al,7 dry corneal epithelium may be easily desquamated and swept away by the normal movement of the eyelids, predisposing patients to painful postanesthetic abrasions or ulcers of the cornea.

One study9 suggests a negative correlation between intraoperative tear production and general anesthesia in dogs. Length of anesthesia has been correlated with progressively decreasing tear production in dogs during and after anesthesia,9,10 but no causal relationship has been established because of the variety of surgical procedures involved, the variable use of anticholinergics and other injectable premedications, and the type of study design used.

Given the reported effects of anticholinergics on aqueous tear production in dogs10 and the possible differences in sympathetic stimulation among inhalant anesthetic types,1,11–13 the authors of the study reported here were interested in the effect of sympathetic tone on perianesthetic aqueous tear production in this study population. Histologically, innervation of canine lacrimal tissue is similar to that in other species,14 so tear

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secretion in dogs is likely regulated by both the sympathetic and parasympathetic nervous systems, as in mice and rabbits. Furthermore, β-blockers attenuate lacrimal gland secretion in rabbits, suggesting that the gland is innervated by β₁-adrenergic receptors. Given these findings, events associated with sympathetic stimulation, such as anesthetic recovery or stress, may substantially increase lacrimal secretion.

The primary objective of the study reported here was to investigate the effect of anesthetic duration and inhalant anesthetic type on intra-anesthetic and post-anesthetic aqueous tear production in clinically normal dogs. A secondary objective was to study the effect of anesthetic recovery quality on postanesthetic aqueous tear production in dogs. The hypothesis was that longer anesthetic duration would cause a lower postanesthetic tear production, tear production would not be affected by type of inhalant anesthesia, and tear production would be greater in dogs with a more active recovery.

**Materials and Methods**

Eight sexually intact female purpose-bred Beagles, approximately 2 to 3 years of age, were used in the study. The protocol was approved by the University of Georgia Animal Care and Use Committee, and husbandry was provided according to established institutional guidelines.

The number of dogs included in the study was based on a post hoc power analysis because variability data for postanesthetic tear production were not available from the literature. The minimum number of dogs needed to achieve an α of 0.05, achieve a β of 0.80, and detect a 5-mm difference in postanesthetic tear production at 2 hours was determined to be 7.

Study subjects had no known underlying systemic disease, and each underwent complete ophthalmic examinations by an experienced individual (PJA), including slit-lamp biomicroscopy, STT, fluorescein stain, and tear film break-up time. Ophthalmic examinations for all 8 dogs were batched into weekly sessions, either Wednesday or Thursday during the second, third, and fourth week of the experiment, such that each dog received a weekly examination over the last 3 weeks of the experiment.

Tear film break-up time (only tested during weekly ophthalmologic examinations in this study) is an indirect means of evaluating the mucin and lipid portions of the precorneal tear film. Tear film break-up time was measured by placing 1 drop of fluorescein on the cornea, manually holding the eyelids open, and evaluating the corneal surface with cobalt blue light (slit-lamp biomicroscope). After the last blink, time to formation of the first evaporative dry spot (dark area) on the cornea was recorded.

Each dog was anesthetized between 7 pm and 11 pm once per week for 4 weeks, with a minimum of 5 days between each anesthetic episode. Anesthetic episodes occurred on Tuesday, Wednesday, or Thursday each week.

Dogs were assigned to 1 of 4 groups by use of a Latin square design: isoflurane for 1 hour (ISO1 group), isoflurane for 4 hours (ISO4 group), desflurane for 1 hour (DES1 group), and desflurane for 4 hours (DES4 group). Over the course of the 4-week experiment, according to a crossover study design, each dog was anesthetized once within each treatment group.

Aqueous tear production was measured in millimeters wetting per minute by use of the STT by placing the tear test strip in the ventral conjunctival fornix approximately one-third of the distance from the lateral to medial canthus. After insertion of the test strip, the eyelids were gently held closed until 1 minute had elapsed, at which time the STT was read and recorded. Both left and right eyes were tested during every time point, in a random sequence. The same person (MKS) administered tear testing for each subject, and prior to each test, the inferior cul-de-sac was gently swabbed with a cotton-tipped applicator to remove accumulated tears and mucus. Tear production was measured at baseline (before anesthetic induction); at 10, 30, and 60 minutes during anesthesia for groups ISO1 and DES1; and again at 2, 3, and 4 hours after induction in the dogs undergoing 4-hour procedures (ISO4 and DES4 groups). Schirmer tear tests were then performed immediately after standing and at 2, 10, and 22 hours after the end of anesthesia. Testing was stopped for each dog after 2 consecutive measurements > 15 mm/min were achieved bilaterally.

Immediately prior to each anesthetic event, body condition score and body weight were determined for each dog by a single observer (MKS) unaware of group assignments. Anesthesia was induced by placing a mask over the dog's muzzle and delivering the maximum vaporizer setting for the agent (5% isoflurane and 18% desflurane) in 2 L of oxygen/min. The dogs were then intubated and positioned in lateral recumbency. Right or left lateral recumbency was determined for each dog randomly by coin flipping. The effect of recumbency on intra-anesthetic tear production was investigated to ensure the equivalency of recumbency and ensure that it should not be included as a covariate in the analysis.

Intermittent positive-pressure ventilation was initiated by use of a volume-cycled ventilator delivering 12 breaths/min to achieve a target end-tidal CO₂ from 35 to 45 mm Hg. Intermittent positive-pressure ventilation was continued until extubation. Oxygen flow was initially delivered at 2 L/min, with the vaporizer set to achieve an end-tidal concentration of 2.0% (isoflurane) or 11% (desflurane) within 20 minutes of induction. These values represent 1.5 times the MAC value for the selected anesthetic. After the target concentration was achieved, oxygen flow was decreased to 0.5 L/min for the remainder of anesthesia. End-tidal agent concentrations were measured with a calibrated gas analyzer by use of a sidestream sampling T-piece located between the endotracheal tube and the Y-piece of the anesthesia circuit. Lactated Ringer's solution was administered IV at 10 mL/kg/h throughout anesthesia. Temperature was measured continuously by use of a probe placed in the thoracic portion of the esophagus and maintained between 36.9° and 37.8°C with a forced-air warming unit.

The eyes of each dog were irrigated with eye-irrigating solution approximately every 10 to 15 minutes throughout anesthesia, but were never irrigated < 10 minutes prior to the next anticipated tear reading. This
protocol was kept consistent for all dogs in every experimental group. No effort was made to close the dogs’ eyes during anesthesia.

At the end of anesthesia, inhalant vaporizers were turned off, and residual inhalant was flushed from the breathing circuit. When dogs began coughing or rejecting the endotracheal tube, IPPV was discontinued, and the dogs were extubated and allowed to lie quietly on a towel placed on the floor. A visual analogue score (0 to 100)22 describing each subject’s behavior during recovery was assigned by a single blinded observer (MKS). A recovery score of 0 corresponded with the smoothest, calmest recovery. After the STT was obtained on standing, a petrolatum ointment was applied to each of the subjects’ eyes to protect the cornea.

Data analysis—Normality was determined by use of the Komogorov-Smirnov test. A repeated-measures ANOVA was performed on the body condition score, body weight, and baseline tearing data. A paired t test was performed to compare left versus right recumbency and left versus right eyes. Linear regression analysis was performed to compare recovery score with postanesthetic tear production. A recovery score of 0 corresponded with the most active, distressful recovery, and a score of 100 corresponded with the smoothest, calmest recovery. After the STT was obtained on standing, a petrolatum ointment was applied to each of the subjects’ eyes to protect the cornea.

<table>
<thead>
<tr>
<th>Inhale</th>
<th>Baseline</th>
<th>10 minutes</th>
<th>30 minutes</th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
<th>Recovery</th>
<th>2 hours</th>
<th>10 hours</th>
<th>22 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>18.2 ± 2.4</td>
<td>1.5* ± 2.0</td>
<td>2.3* ± 2.9</td>
<td>3.4* ± 4.1</td>
<td>2.3* ± 2.5</td>
<td>3.8* ± 2.9</td>
<td>2.5* ± 1.8</td>
<td>10.8 ± 9.9</td>
<td>11.3 ± 10.6</td>
<td>11.0 ± 10.2</td>
<td>11.3 ± 10.7</td>
</tr>
<tr>
<td>Desflurane</td>
<td>19.2 ± 2.5</td>
<td>1.8* ± 3.3</td>
<td>2.0 ± 4.0</td>
<td>4.2* ± 4.1</td>
<td>3.8* ± 2.5</td>
<td>2.5* ± 3.0</td>
<td>1.4* ± 1.5</td>
<td>10.2 ± 10.9</td>
<td>11.1 ± 12.1</td>
<td>11.2 ± 12.3</td>
<td>10.8 ± 11.8</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference from baseline value.

Table 1—Mean ± SD tear production (STT [mm/min]) at various time points in 8 dogs anesthetized with isoflurane or desflurane.

Table 2—Mean ± SD tear production (STT [mm/min]) at various time points in 8 dogs anesthetized with isoflurane or desflurane for 1 or 4 hours.

<table>
<thead>
<tr>
<th>Anesthetic duration (h)</th>
<th>Baseline</th>
<th>Recovery</th>
<th>2 hours</th>
<th>10 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.9 ± 2.2</td>
<td>18.2 ± 2.4</td>
<td>19.3 ± 4.1</td>
<td>19.3 ± 2.3</td>
</tr>
<tr>
<td>4</td>
<td>18.4 ± 2.7</td>
<td>17.5 ± 3.8</td>
<td>19.1 ± 2.6</td>
<td>18.7 ± 2.9</td>
</tr>
</tbody>
</table>

Discussion

To the authors’ knowledge, this study was the first to examine the effect of inhalant anesthetic drugs on intra-anesthetic and postanesthetic aqueous tear production in dogs in the absence of injectable drugs such as hypnotics or tranquilizers. Results indicated that inhalant general anesthetics significantly decreased tear production at a moderately deep plane of anesthesia. General anesthesia performed by use of inhalants alone exerted no substantial lasting effect on postanesthetic tear production in young laboratory Beagles, contrary to the conclusions drawn by authors of other studies8–10 in mixed clinical canine populations.

The decreased intra-anesthetic lacrimation observed in the present study may be attributable to vagolytic or sympathomimetic effects of the inhalant anesthetics, as described.8,11,23,24 Although desflurane has been reported to induce a more pronounced vagolytic effect than isoflurane, this pharmacological effect did not result in any significant difference in intra-anesthetic or postanesthetic tear production. Therefore, it is unlikely that vagolytic activity is associated with tear production during anesthesia in dogs. Vagolytic and sympathetic activity per se were not measured in this study, however, so they cannot be definitively ruled out as factors.

Alternatively, decreased intra-anesthetic lacrimation may be attributed to a blockade of trigeminal function associated with anesthetic depth. As described in previous studies,25,26 lacrimal secretion is largely dependent on afferent sensory function of the trigeminal nerve, followed by an efferent motor response by the facial nerve. The end-tidal inhalant...
concentration was near the target concentration by the first STT reading 10 minutes after induction, indicating that a moderately deep anesthetic plane had been reached by this time. The anesthetic depth may have abolished trigeminal sensory function in a fashion similar to the effect of inhalant anesthetics on other afferent input, thereby disabling a lacrimal response. Once the dog was able to stand, indicating sufficient return of afferent and efferent nerve function, sensory input from the trigeminal nerve was likely restored, resulting in normal tear production. This study did not measure trigeminal or facial nerve activity, so this explanation cannot be verified.

Intra-anesthetic tear production may have also been caused by lagophthalmos. As discussed in a previous publication, lagophthalmos is not a cause of decreased aqueous tear production, but instead is a condition that accelerates tear evaporation via decreased blinking. Blinking is the mechanism by which tears are distributed evenly over the corneal surface, occurring each time the tear film begins to evaporate and a change in temperature is sensed on the corneal surface. Dogs with lagophthalmia may have more rapid evaporation of tear film from the corneal surface because of increased corneal exposure or decreased tear film quality (lipid or mucin). Tear evaporation was not evaluated (eg, by tear film break-up time) during or immediately following anesthesia, however, so STT readings could not be correlated with tear film break-up time data. Further studies are needed to evaluate the effect of lagophthalmos on intra-anesthetic and postanesthetic tear production.

Past studies measuring only basal tear production (STT II) may also support the lagophthalmos explanation for observations made in this study. In the STT II, aqueous tear production is measured 1 minute after topical anesthetic is applied to the corneal surface. The topical anesthetic eliminates contribution from reflex tearing, thus only allowing measurement of basal and residual tears and mimicking the sensory blockade of general anesthesia. The intra-anesthetic STT measurements obtained in this study were less than the basal tear measurements obtained by Gelatt et al in dogs given only topical corneal anesthesia, suggesting that inhalant anesthesia blocks both afferent (sensory) and efferent (motor) pathways to the lacrimal gland.

This study revealed a significant correlation between recovery quality and postanesthetic aqueous tear production. In accordance with our hypothesis, dogs with more active, stressful recoveries typically had higher postanesthetic STT readings than dogs with quiet, peaceful recoveries. We presume that higher sympathetic stimulation associated with emergence from anesthesia with stress may have led to stimulation of lacrimation. Botelho et al suggested the opposite relationship between sympathetic stimulation and decreased aqueous tear production in cats, possibly associated with changes in blood flow to the lacrimal glands. This difference regarding the effect of autonomie stimulation on lacrimal function may indicate species differences or may simply mean that this relationship is incompletely understood. Because our study did not specifically measure indicators of sympathetic tone such as serum catecholamine concentrations, more studies are necessary to clarify the relationship between sympathetic tone and tear production in the perianesthetic period.

Contrary to a previous publication, duration of anesthesia in the present study had no causal relationship with decreased postanesthetic tear production in dogs. This indicates that longer procedures do not necessarily cause a decrease in tear production. It may be that dogs that are anesthetized for a longer period of time in clinical studies receive other drugs to provide a balanced anesthetic protocol and that those other drugs may actually be the factors that affect postanesthetic tear production.

This study's limitations included the potential effects of an ocular ointment applied to the eyes after anesthesia, eye irrigation solution applied during anesthesia, allowance of lagophthalmos, and potentially imperfect masking. To minimize potential injury to the cornea, protective petrolatum-based eye lubrication was administered to the dogs' eyes after the recovery STT measurement was made. It was unknown at the time whether the dogs would have normal tear function, so this decision was made prior to initiation of the study. It is possible that this protocol may have affected subsequent readings.

Intra-anesthetic eye irrigation solution was applied to minimize corneal drying secondary to general anesthesia. Ointment was not administered at this time because it was felt that ointment may affect the STT readings during anesthesia. The ventral cul-de-sac was swabbed before each STT measurement, which would be expected to eliminate the effect of accumulated irritant solution. Regardless of the irrigation protocol, the STT values during anesthesia were extremely low, and thus the irritant likely had a negligible effect on the measurement.

The issue of lagophthalmos was not controlled in this study; no effort was made to close the dogs' eyes during anesthesia, and there was no control group consisting of healthy, lagophthalmic dogs given identical eye wash and STT treatments while awake. However, our ability to hold a dog's eyelids open for an extended period of time (ie, 1 or 4 hours), intermittently irrigating the eye with a saline solution--based solution, swabbing the ventral cul-de-sac, and periodically evaluating STT without allowing the dog to blink, was clearly limited. Future studies investigating the effect of lagophthalmos on intra-anesthetic aqueous tear production may include STT and tear film break-up time measurement in dogs with 1 eyelid taped closed and 1 eyelid left open during anesthesia. Finally, although every attempt was made to mask subjective observers from the chosen inhalant, the inhalants have a distinct odor that may have allowed the observer to surmise the treatment each dog received.

All dogs in this study had decreased intra-anesthetic tear production, regardless of inhalant type or duration, supporting the widely accepted clinical practice of eye lubrication during general anesthesia. Postanesthetic tear production was not affected by inhalant type or anesthetic duration. There was no relationship between recumbency and intra-anesthetic tear production, but a significant correlation was found between active,
stressful recoveries and increased postanesthetic tear production. Results of this study highlight the need for further investigation to determine the effects of serial anesthetic episodes on the mucin and lipid portions of the tear film and the effect of injectable anesthetics on postanesthetic tear production. Future studies may also investigate indicators of vagolytic activity, such as heart rate variability, as they relate to tear production during and after general inhalant anesthesia.

References