

Effects of intramuscular injection of glycopyrrolate on Schirmer tear test I results in dogs

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OBJECTIVE

To determine effects of glycopyrrolate administered IM on Schirmer tear test I (STT I) measurements in dogs.

DESIGN

Prospective clinical study.

ANIMALS

13 client- and staff-owned dogs.

PROCEDURES

For both eyes of each dog, STT I measurements were recorded twice 20 minutes apart (at T1 and T2) and 2 to 4 hours later (at T3). Glycopyrrolate (0.01 mg/kg [0.005 mg/lb]) was administered IM to all dogs (3 dogs received an injection of saline [0.9% NaCl] solution on an earlier occasion), and final STT I measurements were recorded 20 minutes later (at T4). Intraocular pressures, heart rate, and respiratory rate were also recorded at each time point.

RESULTS

Ophthalmic variables did not differ between right and left eyes. In all dogs, variables at T1, T2, or T3 (measurements before glycopyrrolate administration) did not differ; baseline values were therefore defined at T3. At T4, STT I measurements were significantly decreased (mean \pm SD decrease, 67.4 \pm 15.4% [mean actual decrease, 15.8 mm/min]). During the same period, mean heart rate increased by 26.5 \pm 12.0% (mean actual increase, 30.2 beats/min). Glycopyrrolate had no effect on intraocular pressure or respiratory rate. In 5 dogs at 24 hours after glycopyrrolate treatment, STT I measurement in each eye had returned to baseline value. Saline solution treatment (3 dogs) had no effect on any variables.

CONCLUSIONS AND CLINICAL RELEVANCE

In dogs, IM injection of glycopyrrolate resulted in a clinically relevant transient decrease in aqueous tear production. Application of lacrimomimetics beginning at the time of or within 20 minutes after glycopyrrolate premedication is recommended until STT I measurements return to baseline. (*J Am Vet Med Assoc* 2016;248:1262–1266)

In veterinary medicine, the anticholinergics atropine and glycopyrrolate are systemically administered perioperatively to manage bradycardia and vagally mediated arrhythmias and reduce oral and airway secretions.¹⁻⁷ These drugs are relatively nonselective muscarinic receptor antagonists and block cholinergic agents (eg, acetylcholine) at postganglionic parasympathetic sites; therefore, they are often referred to as parasympatholytics.⁸⁻¹¹ When administered systemically, their effects may include sedation (atropine), decreased oral secretions, increased heart rate, increased gastric pH (glycopyrrolate), decreased gastrointestinal motility, and ocular effects (blockade of iris constrictor muscle and ciliary muscle with atropine and decreased lacrimation).¹²⁻¹⁵

Atropine and glycopyrrolate have the same affinity for M1, M2, and M3 muscarinic receptors, but glycopyrrolate is approximately 2 to 6 times as potent.⁹⁻¹¹ Both drugs are rapidly absorbed after IM administration, with onset of cardiovascular effects observed within 5 minutes and peak effects within 10 to 20 minutes.²⁻⁵ After SC administration in dogs, atropine causes a decrease in tear production within 10 minutes and near absolute keratoconjunctivitis sicca develops within 30 to 60 minutes.^{14,16} Although cardiac effects begin to subside within a few hours after either glycopyrrolate or atropine administration in humans and dogs, decreases in tear production in dogs can persist for several days.^{7,17-19} However, the acute effects of glycopyrrolate on tear production in dogs have not been reported, to our knowledge.

Normal corneal metabolism requires a healthy precorneal tear film to deliver oxygen and nutrients to the corneal epithelium. Decreases in lacrimation in animals undergoing anesthesia could contribute to

ABBREVIATIONS

IOP Intraocular pressure
STT Schirmer tear test

corneal disease, and it is recommended that lacrimomimetics be applied to dogs at least every 90 minutes during anesthesia.¹⁶ Because of a potentially superior safety profile, compared with atropine, in terms of gastrointestinal tract adverse effects,⁶ glycopyrrolate is becoming more popular in veterinary medicine, including its use in premedication protocols prior to induction of anesthesia. However, to our knowledge, it has not been determined whether tear supplementation should begin prior to induction of anesthesia in dogs. Therefore, the primary goal of the study reported here was to determine effects of glycopyrrolate administered IM on STT I measurements in dogs. We hypothesized that, similar to atropine, administration of glycopyrrolate would cause a significant and clinically important reduction in STT I measurements within 20 minutes. We also hypothesized that glycopyrrolate would not have a significant effect on IOP.

Materials and Methods

All procedures used in this study were in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.²⁰ Prior to enrollment of dogs in the study, all pet owners were informed of the procedures and gave consent to the use of their pets for purposes of data collection. Each dog underwent a full ophthalmic examination by a board-certified ophthalmologist (REM) to rule out conditions likely to affect aqueous tear production.

Dogs were admitted to the hospital early in the morning of the day of assessment and allowed to acclimate at least 1 hour prior to initiation of data collection. For each dog, STT I measurement and IOP of both eyes, heart rate, and respiratory rate were recorded at 4 time points (T1 to T4): T1 and T2 were 20 minutes apart, as were T3 and T4, whereas there was a variable interval (2 to 4 hours) between time points T2 and T3. Time points T1 and T2 served as control time points to ensure that repeating data collection after 20 minutes did not have any effects on STT I measurement, IOP, heart rate, or respiratory rate. Time point T3 data were defined as baseline values for comparing effects of glycopyrrolate or control (saline [0.9% NaCl] solution) treatment. Immediately following data collection at T3, glycopyrrolate (0.01 mg/kg [0.005 mg/lb]) was administered into the right epaxial muscles of each dog. Therefore, any effects on variables at T4 could be attributed solely to the medication rather than the repeated measurements within a short time. Prior to the glycopyrrolate experiments, a preliminary set of experiments involving 3 staff-owned dogs was performed to ensure repeated measures and injection did not have an effect on the variables of interest. In the preliminary experiments, the aforementioned protocol was followed with the exception that each of the 3 dogs received an IM injection of an equivalent volume of sterile saline solution^a in lieu of glycopyrrolate after data collection at T3. After confirming repeated measures did not have an effect on STT I measurements

by use of saline solution, experiments were then conducted with glycopyrrolate.^b The 3 dogs involved in the preliminary experiments were also included in the glycopyrrolate experiments.

At each time point, STT I measurements were obtained from both eyes of each dog by placing the strip in the lateral half of the lower conjunctival sac with the notch at the level of the lid margin and the strip in contact with the cornea.^c Additionally, IOPs as determined by means of rebound tonometry,^d heart rate, and respiratory rate were also recorded. During the preliminary and main experiments, data collectors were not masked as to whether the dog received an injection of saline solution or glycopyrrolate.

Statistical analysis

A preclinical power assessment was performed. On the basis of published mean STT I measurements in dogs²¹⁻²⁴ and an estimated mean \pm SD STT I measurement of 24 ± 6 mm/min, with statistical analysis of 2-sided alternative, $\alpha = 0.05$, and for a power of 90%, a sample size of 5 dogs would be required to detect a decrease of STT I measurement by 50% and a sample size of 13 dogs would be required to detect a decrease of STT I measurement by 25%.

Frequency tables and descriptive statistics (mean \pm SD and median) for sex, age, STT I measurement, IOP, heart rate, and respiratory rate were analyzed. To test for differences over time, repeated observations were made on the same dogs. In addition, STT I measurement and IOP had repeated measures for the left and right eyes. The experimental design was analyzed with a 2-factor ANOVA with interaction by means of statistical software.^e Specifically, the mixed procedure was used with a repeated option. For the doubly repeated measures, the correlation structure was modeled with a direct product (both unstructured). Multiple comparisons over the 4 time points were made with a Tukey adjustment for multiple testing. For the variables of heart rate and respiratory rate, simpler 1-factor models were used. For these variables, the correlation structure was modeled with compound symmetry. Residuals from the models were examined. Although no extreme values were observed, there were some instances of skewed residuals. The data were reanalyzed with transformations or nonparametric tests. The conclusions were the same as those from the parametric analysis, and for consistency the parametric results are reported. Values of $P < 0.05$ after adjustment were considered significant.

Results

Dogs

Dogs enrolled in the study included 3 Boxers, 3 mixed-breed dogs, and 1 each of Labrador Retriever, Shih Tzu, Samoyed, Jack Russell Terrier, pit bull-type dog, Pug, and Schnauzer. Of the 13 dogs, 1 was a sexually intact male, 6 were spayed females, and 6 were neutered males. Mean \pm SD age of the dogs was 6.4 ± 2.5 years, and age range was from 1.5 to 9.5 years. Eight

of the dogs were admitted to the hospital for ocular surgeries (typically with conditions not likely to affect aqueous tear production but requiring general anesthesia for surgical correction, including lid margin masses that were not causing corneal irritation and minor eyelid margin defects [ectropion] that were not causing corneal irritation). The remaining 5 dogs were staff-owned pets with no ophthalmic abnormalities.

In a preliminary set of experiments in 3 staff-owned dogs, saline solution (control) injections were administered after data collection at T3. There were no effects of control treatment on any of the variables of interest (STT I measurement, IOP, heart rate, and respiratory rate). Although only 3 dogs were used in the preliminary experiments, this was a sufficient number of animals for proof of principle that the variables of interest could be reliably and repeatedly measured at a 20-minute interval without affecting the results. Thirteen dogs (8 client owned and 5 staff owned) were then used in the glycopyrrolate experiments, including the 3 dogs used in the preliminary experiments; inclusion of these 3 animals was unlikely to have introduced any bias to the study findings because the saline solution-related data were not compared with the glycopyrrolate-related data. The preliminary power assessment determined that 13 dogs would be sufficient to be able to detect a difference of at least 25% in STT I measurements; the experimental data from these 13 dogs at the various time points were summarized (Table 1).

For STT I measurements, there was no significant effect of body side (ie, right eye vs left eye). However, the time effect was significant ($P < 0.001$). Pairwise comparisons for the different time points revealed a significant decrease in STT I measurements after glycopyrrolate treatment (ie, at T4), compared with findings at each of the other 3 time points (all prior to administration of glycopyrrolate). There were no significant dif-

ferences among the STT I measurements obtained at T1, T2, and T3. The estimated mean difference in STT I measurement (value at T3 minus value at T4) was 15.8 mm/min (95% confidence interval [adjusting for multiplicity of estimates], 12.1 to 19.5 mm/min). The differences between STT I measurement at T1 and at T2 relative to that at T4 were of the same magnitude. Among the 26 eyes (right and left eyes of 13 dogs) at T3, the lowest STT I measurement was 18 mm/min in 1 eye of 1 dog, and the highest was 35 mm/min in 1 eye of a different dog. At T4 (20 minutes after glycopyrrolate administration), only a single eye still had an STT I measurement > 15 mm/min (30 mm/min at T3 and 23 mm/min at T4); 6 eyes had STT I measurements of 10 to 13 mm/min, 12 eyes had STT I measurements of 6 to 9 mm/min, and 7 eyes had STT I measurements < 5 mm/min. Between T3 and T4, glycopyrrolate treatment decreased STT I measurements by $67.4 \pm 15.4\%$. In 5 staff-owned dogs that were available for follow-up, STT I measurements had returned to baseline (T3 values) 24 hours after glycopyrrolate injection.

For heart rate, the effect of glycopyrrolate treatment was significant ($P < 0.001$). Pairwise comparisons for the different time points revealed a significant increase after glycopyrrolate treatment (ie, at T4), compared with findings at each of the other 3 time points (all prior to administration of glycopyrrolate). There were no significant differences in heart rates obtained at T1, T2, and T3. The estimated mean increase in heart rate (from value at T3 to value at T4) was 30.2 beats/min (95% confidence interval [adjusting for multiplicity of estimates], 22.4 to 38.0 beats/min). The differences between heart rate at T1 and at T2 relative to T4 were of the same magnitude. This corresponded to a mean increase in heart rate between T3 and T4 of $26.5 \pm 12.0\%$. Glycopyrrolate did not have any significant effect on IOP ($P = 0.097$) or respiratory rate ($P = 0.798$).

Table 1—Mean \pm SD STT I measurements, IOP, heart rate, and respiratory rate obtained from 13 dogs before (T1, T2, and T3) and after (T4) IM injection of glycopyrrolate (0.01 mg/kg [0.005 mg/lb]).

Variable	T1	T2	T3	T4	P value (T3 vs T4)
STT I (mm/min)					
Right eye	23.0 \pm 5.4	23.3 \pm 5.7	23.9 \pm 5.0	7.7 \pm 3.3	< 0.001
Left eye	22.8 \pm 5.0	23.5 \pm 5.1	23.3 \pm 4.4	7.9 \pm 5.4	< 0.001
IOP (mm Hg)					
Right eye	15.8 \pm 3.7	15.6 \pm 3.6	16.8 \pm 3.3	15.9 \pm 4.0	0.097
Left eye	15.6 \pm 3.9	15.7 \pm 3.7	16.8 \pm 3.4	15.3 \pm 3.9	0.097
Heart rate (beats/min)	112 \pm 16	116 \pm 12	117 \pm 13	147 \pm 14	< 0.001
Respiratory rate (breaths/min)	32 \pm 11	33 \pm 10	34 \pm 9	33 \pm 10	0.798

For both eyes of each dog, STT I measurement and IOP (measured by rebound tonometry) were recorded twice, 20 minutes apart (at T1 and subsequently at T2). Two to 4 hours later, STT I measurement and IOP were rerecorded (at T3). Glycopyrrolate was then immediately administered IM to each dog, and final STT I measurements and IOPs were recorded 20 minutes later (at T4). Heart rate and respiratory rate were also recorded at each time point. No significant differences were detected among the values obtained at T1, T2, and T3 (in all comparisons, $P > 0.05$). Therefore, only P values are reported for comparisons between T3 (baseline) and T4. Additionally, there was no difference between data for left versus right eyes.

Discussion

In the present study in dogs, glycopyrrolate significantly decreased STT I measurements at 20 minutes after IM administration; therefore, if glycopyrrolate is administered as part of a premedication protocol (or administered during anesthesia), artificial tear supplementation should be administered within 20 minutes. This recommendation applies to all dogs receiving the medication in general and specialty practices.

The present study had a repeated-measures design to ensure there was no effect of repeated data acquisition 20 minutes apart on the variables of interest. In all 13 dogs, there were no changes in STT I measurement, IOP, heart rate, or respiratory rate when measurements were obtained 20 minutes apart (as demonstrated by values T1 and T2) or several hours later (at T3) immediately prior to each dog receiving an injection. Injection of saline solution did not alter any of the variables of interest in 3 study dogs, again indicating that in the glycopyrrolate experiments, the observed effects could be attributed to medication alone and not the repeated-measures experimental design. After administration of glycopyrrolate in all 13 dogs, there was a clinically important decrease in STT I measurement and increase in heart rate, but no effect on IOP or respiratory rate. We hypothesize the aqueous tear production decrease was attributable to an effect on basal and reflex tearing (ie, STT I), rather than just basal tearing (ie, STT II), considering that glycopyrrolate does not have known anesthetic effects. However, testing this hypothesis was beyond the scope of the present study, and results of experiments to measure corneal sensitivity would be required for confirmation.

Effects of the anticholinergic atropine on lacrimation in dogs and cats have been described, with onset of decreased tearing occurring within 10 minutes after SC administration.¹⁴⁻¹⁶ In a retrospective report, Herring et al¹⁷ reported that IM administration of glycopyrrolate to dogs prior to (or during) anesthesia further lowered postanesthetic STT I measurements for up to 24 hours. However, in that study,¹⁷ the first data collection time point was 6 hours after glycopyrrolate administration and no information from the early postadministration phase was provided. In the present study, we evaluated STT I measurements 20 minutes after IM administration of glycopyrrolate and detected approximately two-thirds reduction in tear secretion; therefore, it is possible further decreases could have resulted with time similar to what has been reported following atropine administration. However, because most of the dogs in the present study were undergoing anesthesia for surgery immediately after obtaining the last set of data (at T4), anesthetic induction drugs and inhalation anesthetics that could have affected the results were subsequently administered; hence, it was not possible to evaluate the specific effects of glycopyrrolate for a longer period in our study on client-owned dogs. For 5 staff-owned dogs that were available for recheck examination the following day

(these dogs received only glycopyrrolate and did not undergo anesthesia or receive any other medications), STT I measurements had returned to baseline (T3 values) after 24 hours, a finding that is in agreement with previous study results.¹⁷

Anticholinergic drugs have been implicated in increasing IOP in humans, especially those undergoing spinal surgery.^{25,26} However, a previous study²⁷ in dogs did not reveal an association between glycopyrrolate (0.01 mg/kg) administered IM on pupil diameter or IOP. That study²⁷ included 46 dogs with glaucoma from 2,828 dogs undergoing anesthesia, and only 3 of the 46 dogs had an anticholinergic drug-related increase in IOP. Of those 3 dogs, only 1 received glycopyrrolate, and the transient increase in IOP was attributed to postoperative swelling and not to the medication.²⁷ Thus, the authors concluded no association between parenteral anticholinergic administration and increases in IOP in dogs.²⁷ The results of the present study are in agreement with this finding, in that no significant glycopyrrolate-related effect on IOP was observed within the study period.

In the present study, heart rate was used as a positive control measure. All dogs had an increase in heart rate 20 minutes after glycopyrrolate administration, with a mean increase of approximately 30 beats/min. These results are in general agreement with findings of a previous study⁷ in which IM injection of glycopyrrolate prevented reductions in heart rate. We did not observe an increase in respiratory rate in the dogs following glycopyrrolate administration, which is also in agreement with previous findings.⁷

There are several limitations to the present study. The effects of glycopyrrolate were assessed in isolation, without concurrent systemic administration of any other medications or inhalation anesthetics. Glycopyrrolate is often given as part of premedication protocol with additional medications or administered to treat intraoperative complications after other medications have been administered. Therefore, we did not evaluate whether synergistic or antagonistic effects on tear production occur when glycopyrrolate is combined with other medications. To determine this would have been beyond the scope of the present investigation and would greatly increase the necessary sample size. Another limitation was that data were collected only at a single time point (20 minutes) after administration of glycopyrrolate. It is possible that tear production may have decreased even more substantially with time. After this study time point (T4), client-owned dogs were anesthetized for surgery, and the various medications administered for that purpose would not have allowed determination of the effects of the glycopyrrolate in isolation. Also, only a single IM dose of glycopyrrolate was administered to each dog, and it is unknown whether there is a dose-dependent effect or whether repeated doses of glycopyrrolate have additive effects in this species. Finally, although we only had a limited number of dogs for evaluation, a power calculation prior to the investigation was per-

formed and indicated that the number of dogs in the study was sufficient to be able to detect a decrease in STT I of at least 25%.

In the dogs used in the present study, IM administration of glycopyrrolate resulted in a $67.4 \pm 15.4\%$ decrease in STT I measurements after 20 minutes, and that effect resolved within a subset of the dogs reexamined at 24 hours. Although the decrease in aqueous tear production may be transient, its clinical relevance warrants the use of supplemental lacrimomimetics during the 20-minute interval following glycopyrrolate administration. We therefore recommend a change in veterinary medical practice habits to include the use of lacrimomimetics at the time of glycopyrrolate administration or within 20 minutes thereafter.

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Footnotes

- 0.9% Sodium chloride injection, USP, Abbott Laboratories, Abbott Park, Ill.
- Glycopyrrolate injection USP, 0.2 mg/mL, West-Ward Pharmaceutical Corp, Eatontown, NJ.
- STT strips, Merck Animal Health, Kenilworth, NJ.
- TonoVet, Icare Finland Oy, Vanda, Finland.
- SAS, version 9.2, SAS Institute Inc, Cary, NC.

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