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Authors

Hollingsworth, Steven R
Canton, David D
Buyukmihci, Nedim C
et al.

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Effect of topically administered atropine on tear production in dogs

Steven R. Hollingsworth, DVM; David D. Canton, DVM; Nedim C. Buyukmihci, VMD; Thomas B. Farver, PhD

Summary: *Baseline tear production values were established for both eyes of 19 dogs, using the Schirmer tear test. Atropine sulfate, 1% solution, was administered topically in the left eye of each dog once daily for 14 days. Tear production was then determined for both eyes at 15, 30, 60, 120, 180, 240, and 300 minutes, and 3, 6, 9, 12, and 15 days. A final Schirmer tear test reading was obtained for each eye 5 weeks after the last atropine treatment to check for the possibility of prolonged effect. Both eyes had statistically significant ($P < 0.05$) decrease in tear production that was most marked at 120 minutes after atropine instillation, then returned to baseline values by 300 minutes after instillation. Although atropine was placed in the left eye only, statistically significant difference was not apparent in Schirmer tear test values between the left and right eyes. Tear production continued to decrease in both eyes over time, becoming statistically significant ($P < 0.05$) on day 9. However, on days 12 and 15, tear production in the untreated eye plateaued, but that in the treated eye continued to decrease. Five weeks after the last treatment with atropine, both eyes still had a statistically significant ($P < 0.05$) decrease in tear production, although Schirmer tear test values had increased from day-15 values and appeared to be returning to baseline. Association was not evident between age or body weight and magnitude of response to topically applied atropine.*

Atropine is a common topically applied medication for treatment of ocular diseases in dogs. Systemically administered atropine decreases tear production in dogs,[1-3] and although it is believed that topically applied atropine does the same,[4,5] documentation of this latter effect could not be found. The purposes of the study reported here were to document and quantify the short- and long-term effects of topically applied atropine on tear production in dogs, to determine whether a difference existed in the response of treated and untreated eyes, to determine whether topical administration of atropine has prolonged detrimental effects on tear production, and to ascertain whether the response to atropine in dogs is modulated by age or body weight.

From the Veterinary Medical Teaching Hospital (Hollingsworth) and the Departments of Surgery (Canton, Buyukmihci) and Epidemiology and Preventative Medicine (Farver), School of Veterinary Medicine, University of California, Davis, CA 95616.

Materials and Methods

Dogs—Nineteen dogs (6 males, 13 females; age ranging from 1 to 8 years), belonging to students, staff, and faculty at the teaching hospital were studied. Dogs currently were not being given any medication and were judged, by biomicroscopy and indirect ophthalmoscopy, to be free of any ocular condition that would adversely affect lacrimal function. Incidental findings included focal cataracts (n = 2), chorioretinal scars (n = 1), mild distichiasis (n = 3), and remnants of the pupillary membrane on the anterior lens capsule (n = 4).

Study design—Each dog was weighed, and 2 baseline Schirmer tear test[3] (Schirmer I tear test) readings were taken, using standard, commercially available Schirmer tear test strips.[a] Because Schirmer tear test strips and the subsequent values obtained can vary among manufacturers and lot numbers,[6] the strips used all came from the same source and lot. At least a 30-minute interval was used between the 2 baseline readings. After the second baseline reading, 1 drop of 1% atropine sulfate solution[b] was instilled in the left eye. Subsequent tear production readings were taken for both eyes at 15, 30, 60, 120, 180, 240, and 300 minutes after instillation (short-term study). This was considered day 1 of the study. For the next 13 days (2 through 14), each dog was given 1 drop of 1% atropine sulfate solution in the left eye once a day, between 6 and 9 AM. On days 3, 6, 9, 12, and 15, dogs were returned to the teaching hospital between 6 and 9 AM, and tear production was measured for both eyes (long-term study) before they were given their daily dose of atropine (no treatment on day 15). Seven weeks after the study was begun (5 weeks after discontinuance of atropine), final determination of tear production was made for both eyes.

[a]IOLAB Pharmaceuticals, Claremont, Calif.
[b]Allergan Pharmaceuticals, Irvine, Calif.

Table 1—Schirmer tear test (STT) values for the short-term study

Time	Left eye STT (mm/min)	Decrease from baseline, left eye (%)	Right eye STT (mm/min)	Decrease from baseline, right eye (%)
Baseline	23.03[a]	...	23.29[a]	...
15 min	21.53[a,b,c]	6.5	21.47[a,b,c]	7.8
30 min	19.21[c,d,e]	16.6	20.00[c,d,e]	14.1
60 min	17.84[e,f]	22.5	18.53[e,f]	20.4
120 min	17.26[f]	25.0	17.95[f]	22.9
180 min	18.84[d,e,f]	18.2	19.26[d,e,f]	17.3
240 min	20.32[b,c,d]	11.8	20.21[b,c,d]	13.2
300 min	21.74[a,b]	5.6	21.84[a,b]	6.2

Means that have one superscript in common are not statistically significantly different from each other with a level of significance of 5% over all comparisons, using Tukey's method for pairwise comparisons of means.

Table 2—Schirmer tear test values for the long-term study, left eye

Time	STT (mm/min)	Decrease from baseline (%)
Baseline	23.02[a]	...
Day 3	22.74[a]	1.1
Day 6	22.74[a]	1.1
Day 9	20.37[b]	11.5
Day 12	20.32[b]	11.7
Day 15	19.05[b]	17.2

See Table 1 for key.

Table 3—Schirmer tear test values for the long-term study, right eye

Time	STT (mm/min)	Decrease from baseline (%)
Baseline	23.29[a]	...
Day 3	23.00[a,b]	1.2
Day 6	22.42[a,b]	3.7
Day 9	20.68[c]	11.2
Day 12	21.63[b,c]	7.1
Day 15	20.89[c]	10.3

See Table 1 for key.

Analysis of data—Four specific responses were analyzed statistically. Repeated-measures analysis of variance was the statistical method used to evaluate the reaction of the left (treated) eye to the right (nontreated) eye, the reaction of each eye to its own baseline value, and the 5-week period of testing.[7] Pairwise comparisons of means were made, using Tukey's procedure.[8] Regression analysis was used to determine the significance of age or body weight on the extent of the response to topically applied atropine.

Results

In the short-term study, statistical difference was not observed in the response between the right and left eyes at any of the measurement times. Both eyes had significant ($P < 0.05$) decrease in tear production within 30 minutes after unilateral instillation of atropine. This decrease reached maximum at 120 minutes after atropine instillation, then returned to baseline values by 300 minutes (Table 1; Fig 1).

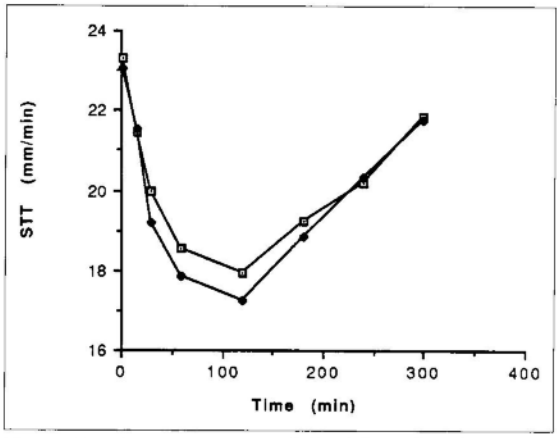

Figure 1—Tear production of the left and right eyes at measurement times in response to atropine applied topically in the left eye. The decrease in tear production reached its maximal extent at 120 minutes after atropine instillation, then returned to baseline by 300 minutes after instillation. Differences between right and left eyes were not statistically significant. STT = Schirmer tear test. —□— = right eye. —◆— = left eye.

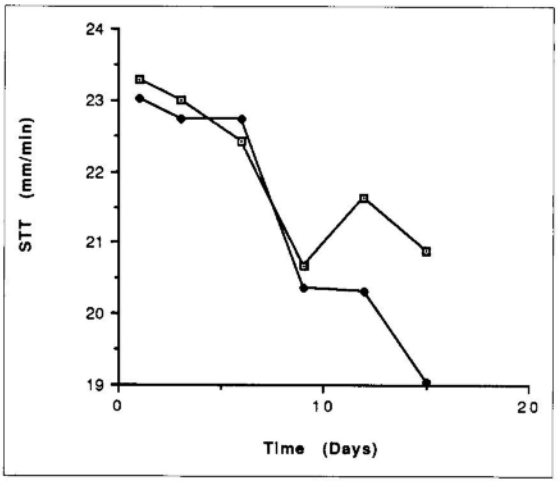

Figure 2—Tear production of the left (atropine-treated) and right (untreated) eyes decreased similarly through day 9, at which time the tear production of the left eye continued to decrease while tear production of the right eye leveled out. See Figure 1 legend for key.

In the long-term study, tear production of the left eye had decreased significantly (compared with the baseline value) by day 9 ($P < 0.05$) and continued to decrease until day 15, when atropine was discontinued (Table 2; Fig 2). Tear production by the right eye had also decreased significantly (compared with its baseline) by day 9 ($P < 0.05$), but then seemed to plateau (Table 3; Fig 2). When the left and right eyes were compared with each other for tear production, statistical difference was not apparent in response through day 9, but on days 12 and 15, tear production of the left eye was significantly ($P < 0.05$) less than that of the right eye.

Table 4—Schirmer tear test values for the 5-week posttreatment evaluation

Time	Left eye, STT (mm/min)	Right eye, STT (mm/min)
Baseline	23.03	23.29
Five weeks after treatment	21.84	22.16

See Table 1 for key.

At the 5-week evaluation, statistically significant difference was not observed between Schirmer's tear test values for the left and right eyes. Whereas tear production of both eyes was increasing toward the initial baseline readings, statistically significant ($P < 0.05$) decrease in tear production was still evident (Table 4). Association was not found between age or body weight and magnitude of the response to atropine.

Discussion

Lacrimation can be classified into 2 categories: basic and reflex. Basic tear production is a process in all vertebrates that spend at least part of their life on land. It occurs during waking and nonwaking hours.[9] The specific neuronal control of this type of lacrimation is not understood completely but can be affected by autonomic agents, such as parasympathetic antagonists (eg, atropine). Reflex lacrimation is a response to peripheral or central stimulation. Peripheral activation of this reflex is the result of noxious stimulation of the sensory nerve endings of the adnexa, conjunctiva, cornea, or uvea that arise from the ophthalmic branch of the fifth cranial nerve. The efferent portion is distributed principally via parasympathetic nerve fibers, although some sympathetic contribution exists.[10,11] The Schirmer tear test measures basic and reflex lacrimation stimulated by the tip of the test strip. Of all the incidental findings during the initial ophthalmic examinations, only distichiasis could potentially cause a change in lacrimation. All 3 dogs with distichiasis, however, had only 1 or 2 distichiae, and these were not in contact with the cornea or conjunctiva. Central stimulation of reflex lacrimation can be psychogenic, which is thought to exist only in human beings, or retinal. The retinal component of reflex lacrimation, which is initiated by light stimulating the retina, combines with basic lacrimation to constitute normal tear production during waking hours in healthy animals.[9]

Our results suggest that topically applied atropine causes transient decrease in tear production in dogs, beginning with the first application and possibly persisting for several weeks after atropine is discontinued. In the short-term study, both eyes responded in statistically identical manner, even though atropine was instilled only in one eye. This indicates that topically applied atropine may have a systemic effect on tear production over the short term. This similarity of the response of both eyes continued through the ninth day of the long-term study, at which time tear production by the treated eye became significantly less than that by the untreated eye. This indicates that topically administered atropine may have local effect that becomes more pronounced over time. It was surprising that a persistent significant decrease in tear production was detectable 5 weeks after atropine treatment was stopped. However, we believe that Schirmer tear test values would eventually reach the initial, baseline values, and that topically administered atropine alone probably does not induce a permanent decrease in tear production.

There were 3 major limitations to our study. We assumed that, after each daily dose of atropine, tear production would go through the same decrease and increase as was seen after the first application of atropine. We did not attempt to document this during the course of the long-term study. Also, our study was designed only to document the response to topically administered atropine, not to explain the underlying mechanisms of this response. Although it is likely that the systemic nature of the response to topically applied atropine was attributable to uptake of the drug into the general circulation and subsequent spread to the glandular tissue of the contralateral (right) eye, a central neuronal control mechanism, as has been hypothesized in the control of intraocular pressure,[12] is possible. Finally, because of difficulties in acquiring adequate sample size, we did not have a specific control group. We recognize that topically applied atropine causes changes in the untreated eye, rendering that eye inadequate as a control. Despite these limitations, we believe our results are suggestive that atropine was responsible for the decrease in tear production. It seems unlikely that extraneous factors could account for the decrease and subsequent increase in baseline Schirmer tear test values detected in the short-term study or the differences in tear production detected between the eyes on days 12 and 15 of the long-term study.

Because atropine is a commonly used ophthalmic drug, it was our intent to simulate a standard, clinical atropine treatment regimen, which is usually once a day. Although we were able to detect a statistically significant decrease in tear production, it is doubtful that this decrease would have any clinical effect in a dog with normal Schirmer tear test values prior to topical administration of atropine. However, it may be prudent to do Schirmer tear tests on all dogs being considered for long-term atropine administration. Dogs with low normal pretreatment values could be at risk of developing problems secondary to insufficient tear production when treated topically with atropine for long periods. This persistent effect of atropine on tear formation becomes especially relevant when planning a treatment regimen for a dog that is starting with borderline Schirmer tear test values. This may be exacerbated by more than one daily topical application of atropine. Because of the po-

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tential for problems, it may be appropriate to do Schirmer tear tests at least once a week on dogs being treated with topically administered atropine.

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Efficacy of an in-feed preparation of ivermectin against endoparasites and scabies mites in swine

In 2 trials, the efficacy of an in-feed preparation of ivermectin was evaluated in 40 pigs naturally infected with endoparasites and *Sarcoptes scabiei* var *suis*. Treated pigs (n = 10 in each trial) were fed a ration containing 2ppm ivermectin for 7 days, followed by consumption of a nonmedicated ration for the duration of the trial. Control pigs (n = 10 in each trial) were fed a complete, nonmedicated ration for the duration of the trial. Pigs in trial A were monitored for 14 days after treatment; those in trial B were monitored for 35 days after treatment.

In trial A, treatment efficacy of ivermectin was 100% against *Ascaris suum, Physocephalus sexalatus, Oesophagostomum dentum, O brevicaudum*, 99.8% against *Ascarops strongylina*, 90.9% against *Trichuris suis*, and 13.1% against *Macracanthorhynchus hirudinaceus*. At the end of the trial, statistically significant ($P < 0.05$) differences were observed between numbers of treated and control pigs infected with *A suum, Ascarops strongylina*, and *Oesophagostomum* spp. On posttreatment day 14, *S scabiei* were not found in any scrapings taken from treated pigs, but were found in scrapings from 3 of 10 control pigs. The number of infested pigs in the treatment group was not statistically different from the number of infested pigs in the control group.

In trial B, treatment efficacy was 100% for *A suum* and *Metastrongylus* spp; 96.9% for *Ascarops strongylina;* and 76.9% for *M hirudinaceus*. At the end of the trial, statistically significant ($P < 0.05$) differences were evident between numbers of treated and control pigs infected with *A suum, Ascarops strongylina*, and *Metastrongylus* spp.

On posttreatment days 7, 21, and 35, *S scabiei* were not found in scrapings taken from treated pigs. On posttreatment days, 7, 21, and 35, *S scabiei* were found in scrapings from 8 pigs, 6 pigs, and 1 pig, respectively, whereas live mites were not found in scrapings taken from treated pigs on those days. Statistically significant ($P < 0.05$) differences were evident between the numbers of infested pigs in the treated and control groups on days 7 and 21.—*Nicholas D. Primm, William F. Hall, Joseph A. DiPietro, et al in Am J Vet Res 53 (April 1992).*