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Effect of topical pilocarpine treatment on tear production in dogs

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Summary: *Tear production, evaluated every 2 hours from 8 AM to 8 PM by use of the Schirmer tear test over a 3-day period, was not significantly different between left and right eyes in 12 dogs. However, a significant diurnal pattern was evident. Tear production was lowest at midday and highest in the late afternoon/early evening. After pilocarpine HCl ophthalmic solution (0.25, 1.0, or 2.0%; 1 drop) was administered topically to the left eye of each dog at 7 AM on days 4, 6, and 8, respectively, tear production was determined for both eyes every 2 hours from 8 AM to 8 PM on the day of treatment. Analysis of tear values between eyes and between each eye's treatment and pretreatment values did not reveal significant change for the treated eye, but tear production was significantly less in the untreated eye, compared with its pretreatment values and with values in the treated eye. On day 10 (48 hours after the last treatment), tear production values were not significantly different between left and right eyes, and for both eyes, were not significantly different from the mean pretreatment tear production values. Topical application of 0.25, 1.0, or 2.0% pilocarpine HCl consistently caused blepharospasm, conjunctival hyperemia, and miosis of the treated eye, without significant increase in tear production. We concluded that topical application of pilocarpine, at the concentrations used, may have little value in treating disorders involving reduced tear production.*

Pilocarpine, a direct-acting (cholinergic) parasympathomimetic drug, has been advocated for oral use to stimulate tear production in canine patients with keratoconjunctivitis sicca[1-6] and appears to be effective when given through this route. It also has been advocated for topical use in the treatment of this condition.[1-3,7] Pilocarpine is commonly mixed with artificial tears, antibiotics, and acetylcysteine, giving a final concentration of 0.25%, and applied hourly until clinical improvement is seen.[2,3,7] It also is used alone at 0.25 or 1% concentrations, applied every 4 to 12 hours.[1] Although it appears to be widely used, reports of studies evaluating the effectiveness of topically applied pilocarpine in stimulating tear production were not found in a review of the literature. Because pilocarpine is a potentially serious irritant when used topically,[4,7-10] the purpose of the study reported here was to determine whether topical application of pilocarpine had any lacrimatory effect which would outweigh the potential risks.

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Materials and Methods

Twelve dogs (4 sexually intact males, 6 castrated males, 2 spayed females; age, 2 to 12 years) belonging to students and staff were used. Two dogs were receiving oral filaricide[a] treatment once per month. The dogs were determined, by biomicroscopy and indirect ophthalmoscopy, to be free of any ophthalmic condition that would adversely affect lacrimal function. An incidental finding which might have affected tear production was mild distichiasis in 2 dogs. In neither case, however, were cilia observed to be in contact with cornea.

All dogs were housed under similar conditions. The mean ambient temperature and relative humidity were recorded concomitant with Schirmer tear test (STT) measurements. Prior to treatment, STT[11] was done on both eyes, without topical anesthetic treatment, every 2 hours from 8 AM to 8 PM, daily for 3 days. This method was chosen because it is a common and practical method of evaluating tear production in dogs. Because STT strips and their absorptive capacity can vary between manufacturers and lot numbers,[12] all strips used were from the same manufacturer and lot.[b]

On days 4, 6, and 8, 1 drop of pilocarpine HCl, as a 0.25, 1.0, or 2.0% solution,[c] respectively, was instilled in the left eye of each dog at 7 AM. These concentrations were chosen to include and exceed the recommended concentrations for topical use.[1-3,7] One instillation was deemed appropriate because the main objective of the study was to determine whether topically administered pilocarpine had any effect on lacrimation. Only 1 eye of each dog was treated, to determine whether a contralateral effect existed. An STT was done on each eye

[a]Heartguard, MSD-Agvet, Rahway, NJ.
[b]IOLAB Pharmaceuticals, Irvine, Calif.
[c]Isopto Carpine, Alcon Laboratories, Fort Worth, Tex.

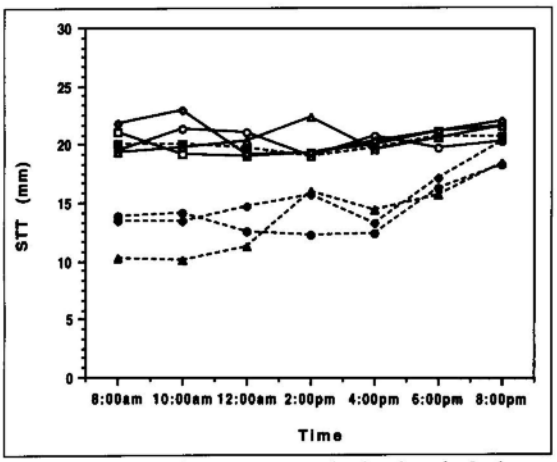

Figure 1—Mean Schirmer tear test (STT) values for both eyes in 12 dogs before and after topical treatment with various concentrations of pilocarpine solution. Pretreatment, left (—□—); pretreatment, right (---■---); 0.25% pilocarpine, left (—○—); 0.25% pilocarpine, right (---●---); 1.0% pilocarpine, left (—△—); 1.0% pilocarpine, right (---▲---); 2.0% pilocarpine, left (—◇—); and 2.0% pilocarpine, right (---◆---).

every 2 hours from 8 AM to 8 PM on each day of treatment.

On day 10 (48 hours after the last treatment), an STT was done on each eye every 2 hours from 8 AM to 8 PM to determine any residual effects of pilocarpine treatment. A 48-hour interval between treatments was chosen because the effects of pilocarpine on pupillary aperture and intraocular pressure are not important 48 hours after topical application in the dog.[8]

Repeated-measures ANOVA[13,14] was used to evaluate tear production by day, hour, and eye; to compare the left (treated) eye with the right (untreated) eye; and to compare treated and pretreatment values in each eye. When a variable was significantly different (day, hour, and treatment), Tukey's method for pairwise comparisons of means was used, with significance of 5% over all comparisons.[13]

Results

A significant difference was not found between pretreatment responses from the left and right eyes. Pretreatment daily mean STT values ranged from 19.1 to 20.9 mm in 1 minute. Range of individual pretreatment STT values was 4 to 28 mm; however, only 3 of 12 dogs had 4 or fewer STT values (out of 42) that were < 10 mm. Significant ($P < 0.05$) diurnal fluctuation in pretreatment tear values was observed with lowest values at midday (12 and 2 PM) and highest values in the late afternoon/early evening (6 and 8 PM; Fig 1). Mean ambient temperature was 25.2 C (range, 14.4 to 34.4 C) and peaked at about 4 PM each day. The mean relative humidity was 43.3% (range, 24.8 to 74.7%) and was lowest at approximately 4 PM each day.

After treatment with pilocarpine, STT values in the treated (left) eye were not significantly different from pretreatment values over all time points for each concentration of pilocarpine. In the untreated (right) eye, STT values decreased significantly ($P < 0.0002$) from pretreatment values at every time point with each concentration of pilocarpine, and were significantly ($P < 0.05$) lower than those in the left eye at every time point, except 8 PM, with each concentration of pilocarpine (Table 1; Fig 1). A trend for STT values in the right eye to gradually return toward pretreatment values by 8 PM was evident. On day 10, significant difference was not found between left and right eyes (mean, 20 mm for each eye), nor were the values different from mean pretreatment values.

Table 1—Mean Schirmer tear test values in the right (untreated) eye in 12 dogs before and after topical treatment with various concentrations of pilocarpine solutions

		% Pilocarpine		
Time	Pretreatment	0.25	1.0	2.0
8 AM	20.1	13.8^{bc}	10.3^{c}	13.4^{b}
10 AM	20.0	14.2^{bc}	10.1^{c}	13.4^{b}
12 AM	19.7	12.6^{bc}	11.2^{bc}	14.7^{b}
2 PM	19.0	12.2^{c}	16.0^{ab}	15.7^{ab}
4 PM	19.7	12.4^{bc}	14.4^{abc}	13.3^{b}
6 PM	20.8	16.3^{ab}	15.7^{ab}	17.1^{ab}
8 PM	20.7	18.3^{a}	18.5^{a}	20.3^{a}

All values are in millimeters. For each treatment, means that do not have at least 1 superscript in common are significantly ($P < 0.05$) different, using Tukey's method for pairwise comparisons of means.

In all treated eyes, administration of pilocarpine induced mild blepharospasm and moderate conjunctival hyperemia within a few minutes and miosis within an hour. The effect did not appear to vary with different concentrations of pilocarpine. Blepharospasm and conjunctival hyperemia persisted for about 4 to 6 hours, and miosis was evident for about 8 to 12 hours. Similar irritative effects were not seen with STT measurements alone.

Discussion

Lacrimation can be divided into basic (basal) and reflex secretion.[11,15] Basal tear production is continuous for all vertebrates that spend at least part of their life on land.[16] Reflex lacrimation is a response to central or peripheral stimulation. Central stimulation of reflex tearing can be retinal or psychogenic, the latter of which is thought to exist only in human beings. Retinal activation of reflex lacrimation requires light stimulation of the retina which, along with basal lacrimal secretion, constitutes normal tear production during waking hours in healthy animals. Peripheral activation of reflex lacrimation arises from noxious stimulation of sensory nerve endings within the adnexa, conjunctiva, cornea, uvea, or nasal mucosa (via the maxillary branch of the trigeminal nerve).[17] The STT is a measure of basal and reflex lacrimation.[18] Reflex lacrimation stimulated by the tip of the test strip may vary with corneal sensitivity, which has been shown to correlate with skull type in dogs.[19] We

believe that any reflex lacrimation induced by the test strip was consistent throughout the study for treated and untreated eyes.

The pretreatment daily mean STT values were consistent with other reports.[20-22] The diurnal effect for STT values may have been attributable to an internal rhythm. The lowest STT values (at 12 and 2 PM) did not coincide with the nadir for relative humidity or the peak in ambient temperature (4 PM). The highest STT values (at 6 and 8 PM) did not coincide with the peak for relative humidity and the lowest ambient temperature (at 8 AM). Therefore, temperature and relative humidity seem unlikely to have had an appreciable effect on the dogs' tear values. In human beings, low humidity and high ambient temperature also have been shown not to influence STT values.[23] Diurnal effect has not been observed in human beings, except for decreased tear formation during nonwaking hours (ie, lack of reflex component).[24]

The recommendation for topical use of pilocarpine in the treatment of keratoconjunctivitis sicca probably is based on pilocarpine's known direct stimulatory effect on the lacrimal gland.[25] Although this effect is evident with oral treatment,[4] our study failed to reveal any lacrimatory effect through topical application.

Because pilocarpine causes ocular irritation, assuming that this effect may lead to increased lacrimation through stimulation of the peripheral nerve endings (reflex secretion) would be logical. However, our study failed to reveal a significant difference between treatment and pretreatment tear values. Therefore irritation of the treated eye did not seem to be associated with concomitant lacrimation. Because pilocarpine does not have an anesthetic effect on the cornea, a related decrease in sensitivity to the test strip in treated eyes, with reduction in that component of secretion, seems unlikely.

Contrary to our expectations, we found a decrease in tear production in the untreated eyes. This contralateral decrease in tear production has not been previously reported for pilocarpine. A contralateral effect has been detected in intraocular pressure with topically applied pilocarpine[26,27] or other antiglaucoma agents,[26] as well as for tear production with topically applied atropine.[18] These previously documented contralateral effects remain unexplained. The finding of a contralateral decrease in tear production in our study was difficult to explain because lacrimal regulation is multifactorial, and complex, and has not been fully elucidated. Many factors, such as various peptides, hormones (prolactin,[28] androgens[29]), β-adrenergic agonists, and cholinergic agonists influence lacrimation,[30] adding to the complexity.

In our study, we could not determine whether a systemic, central, or local regulatory feedback mechanism caused the decrease in contralateral lacrimation. The pilocarpine may have been absorbed systemically and exerted an inhibitory effect on the opposite eye, via the bloodstream. However, this mechanism is unlikely, given the known stimulatory effect when administered orally, unless it is related to concentration. A central neuronal reflex that exerted an inhibitory, probably sympathetic, effect on the opposite eye is more likely.[31] That irritation of the treated eye induced a contralateral decrease in tear production also seems unlikely. In human beings, an irritative effect in 1 eye not only stimulates lacrimation in that eye, but also tends to increase lacrimation in the opposite eye.[24] To our knowledge, no one has studied the ipsilateral and contralateral effects of an inert (ie, without pharmacologic effect) topical ocular irritant on lacrimation in dogs.

We concluded that topical pilocarpine treatment may have little value in treating disorders involving a decrease in tear production, and has the potential for causing ocular irritation. Any beneficial effect of pilocarpine used in this manner may be attributable more to the wetting effect of the vehicle or of the other solutions when used as a mixture. We suggest that artificial tears alone, cyclosporine drops,[5,32,33] or systemic pilocarpine treatment[1-6] may be more appropriate and reliable methods of treating keratoconjunctivitis sicca.

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