Effects of oral administration of diphenhydramine on pupil diameter, intraocular pressure, tear production, tear film quality, conjunctival goblet cell density, and corneal sensitivity of clinically normal adult dogs

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Objective—To evaluate the effects of oral administration of diphenhydramine on pupil diameter, intraocular pressure (IOP), tear production, tear film quality, corneal sensitivity, and conjunctival goblet cell density (GCD) in clinically normal adult dogs.

Animals—12 healthy adult dogs.

Procedures—All dogs received diphenhydramine (2.2 mg/kg, PO, q 12 h) for 21 days. Conjunctival biopsy samples were obtained immediately before (day 1) and after (day 21) treatment with diphenhydramine and conjunctival GCDs were determined. Gross ophthalmic examinations and fluorescein staining of corneas were performed, and pupil diameter, corneal sensitivity, IOP, tear production, and tear film breakup time were determined prior to administration of diphenhydramine on days 1 through 5 and on day 21; pupil diameter and IOP measurements were repeated on each of those days at 20 and 40 minutes and 1, 3, 6, and 8 hours after administration of diphenhydramine. Data were analyzed to detect differences among values for dogs.

Results—Clinically important increases in pupil diameter were not detected after administration of diphenhydramine to dogs. Day 1 corneal sensitivity and tear film breakup time for dogs were significantly higher than day 21 values for those variables.

Conclusions and Clinical Relevance—Results of this study suggested that oral administration of diphenhydramine to healthy adult dogs was not likely to acutely induce glaucoma or keratoconjunctivitis sicca. However, effects of diphenhydramine in dogs with keratoconjunctivitis sicca or primary glaucoma or dogs genetically predisposed to development of those conditions were not determined. Administration of diphenhydramine to dogs decreased corneal sensitivity and tear film breakup time, although these effects were not clinically important. (*Am J Vet Res* 2012;73:1983–1986)

Allergic responses involve a cascade of events coordinated by mast cells. These activated mast cells release mediators, including histamine, that cause clinical signs of allergic inflammation via activation of inflammatory cells. Histamine released from mast cells binds to H1 receptors on nerve endings. The clinical effects of this process in dogs with atopy or allergic dermatitis of any other type are pruritus and dermatitis. Histamine may also bind to H1 and H2 receptors in conjunctival vasculature, causing vasodilation and hyperemia characteristic of allergic conjunctivitis.[1] Antihistamine drugs (H1 and H2 receptor antagonists) are commonly administered systemically or topically to eyes of humans to relieve ocular signs of allergies, including conjunctival hyperemia, epiphora, chemosis, blepharitis, and pruritis.[2] Topical or systemic administration of antihistamines can cause dilation of pupils, reduce tear production, or decrease tear film quality in humans.[3,4] Pupillary dilation may cause an increase in IOP in humans with glaucoma or those with a predisposition to glaucoma; therefore, drugs such as antihistamines that cause pharmacological mydriasis are not typically administered to such patients.[3,5,6]

Abbreviations

CTT	Corneal touch threshold
GCD	Goblet cell density
IOP	Intraocular pressure
KCS	Keratoconjunctivitis sicca
STT	Schirmer tear test
TBUT	Tear film breakup time

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Antihistamines are commonly administered orally to dogs as adjunctive treatments for atopic dermatitis and may be administered topically for treatment of allergic conjunctivitis.[7] The objective of the study reported here was to determine whether administration of antihistamines affects various ophthalmologic variables in dogs. We hypothesized that oral administration of antihistamines would cause changes in pupil diameter, IOP, tear production, conjunctival GCD, corneal sensitivity, and tear film quality of eyes of healthy dogs.

Materials and Methods

Animals—Twelve privately owned adult dogs without signs of systemic or ophthalmic disease that were patients at a large multispecialty veterinary hospital were recruited for the study on a voluntary basis. Each owner signed an informed consent form that disclosed the planned study procedures. Medical and ophthalmologic histories were obtained from owners via questionnaires. Institutional approval for the study was not obtained because the private multispecialty veterinary hospital at which the study was performed did not have an institutional oversight committee. During the study, dogs were monitored by trained veterinary ophthalmology staff. For each dog, serum biochemical analyses and a CBC and serum thyroid assay were performed to detect systemic diseases. Results of these tests were unremarkable for all dogs included in the study.

Study design—The right and left eyes of each dog were examined by a board-certified veterinary ophthalmologist (GLL). Ophthalmic examinations included performance of slit-lamp biomicroscopy, indirect ophthalmoscopy, pupillometry (with a manually operated pupillometer), corneal esthesiometry[a] (to determine CTT [as an estimate of corneal sensitivity]), STT (by use of an STT-1 test for measurement of the trigeminal-facial reflex and basal tear secretion [performed without topical anesthesia]), corneal fluorescein staining, TBUT testing (for determination of tear film quality), rebound tonometry,[b] and direct gonioscopy (for evaluation of iridocorneal angle conformation).[2] Dogs with an IOP > 25 mm Hg, a difference in IOP of > 4 mm Hg between the right and left eyes, abnormal gonioscopy results, or clinical signs of anterior uveitis were excluded from the study. Other exclusion criteria included a STT result of < 15 mm of wetting/min, TBUT < 20 seconds, corneal staining with fluorescein, or corneal ulceration or blepharospasm detected via ophthalmic examination.

Dogs with clinical examination abnormalities likely to affect values of measured ophthalmologic variables (pupil diameter, TBUT, and results of tonometry, STT, and corneal sensitivity testing) or abnormalities that would prevent determination of these variables were also excluded from the study. For example, dogs with age- or breed-related iris atrophy of sufficient severity to affect pupil diameter, shape, or light response (in the opinion of the examining board-certified veterinary ophthalmologist) were excluded. However, dogs with subclinical trichiasis or distichiasis, mild corneal dystrophy or degeneration, minor corneal scarring, nuclear sclerosis, minor cataracts, mild iris atrophy, vitreal degeneration, vitreal opacities, or retinal degeneration were not excluded from the study. Dogs with corneal abnormalities were included in the study only if those abnormalities were not severe enough to preclude accurate determination of pupil diameter. Only data for dogs for which both eyes met inclusion criteria were included in the study.

Diphenhydramine[c] (2.2 mg/kg, PO, q 12 h for 21 days)[8] was prescribed for all dogs in the study. A conjunctival biopsy sample was obtained by use of forceps and scissors from the lower nasal conjunctival fornix (one of the areas of highest conjunctival GCD in dogs[9]) of each eye of each dog immediately prior to administration of the first dose of diphenhydramine (day 1). Another conjunctival biopsy sample was obtained from each eye of each dog from the same sites after the last dose of diphenhydramine was administered (day 21). Proparacaine[d] was administered topically as a local anesthetic to eyes prior to collection of conjunctival biopsy samples. Immediately after collection, conjunctival biopsy samples were placed in jars containing 10% formalin. Pretreatment and posttreatment conjunctival biopsy samples were submitted to a board-certified veterinary pathologist (PL) for histologic determination of conjunctival GCD.

For each dog, ophthalmologic evaluation started at 8 AM on days 1 through 5 of the study. Gross ophthalmic examination (performed by use of the modified McDonald-Shaddock scheme)[10] and pupillometry, corneal esthesiometry, rebound tonometry, corneal fluorescein staining, and STT and TBUT tests were performed.[10] On each of those days (days 1 through 5), dogs were evaluated immediately prior to administration of the first dose of diphenhydramine for that day, which was administered by one of the investigators. Performance of gross ophthalmic examinations and pupillometry and tonometry were repeated at 20 and 40 minutes and 1, 3, 6, and 8 hours after administration of the first dose of diphenhydramine on each of those days (days 1 through 5). On each of the first 5 days of the study, the second doses of diphenhydramine were administered to dogs by owners approximately 12 hours after the first doses had been administered. Time of diphenhydramine administration was recorded daily by owners, and administration times were evaluated by the investigators; diphenhydramine administration times were consistent, and no dogs were excluded from the study because of owner noncompliance. On days 6 through 21 of the study, diphenhydramine was administered to dogs every 12 hours by owners. Dogs were reevaluated by the investigators on day 21 of the study via the same procedures that were used to evaluate dogs on days 1 through 5 of the study.

Statistical analysis—Ophthalmologic variables were evaluated for each eye of each dog, and values were analyzed to determine differences among times (days 1 through 5 and day 21). Data were analyzed to identify changes in pupil diameter, IOP, aqueous tear production (determined via STT-1 tests), tear film quality (determined via TBUT tests), and CTT at each time versus baseline values obtained on day 1 immediately prior to administration of the first dose of diphenhydramine. Data regarding GCDs in conjunctival biopsy samples obtained on days 1 and 21 were also analyzed.

A repeated-measures profile analysis was performed to compare data regarding mean pupil diameters for each eye of each dog on each evaluation day (days 1 through 5 and day 21). Paired samples *t* tests were performed to determine significant differences among TBUTs and CTT values for dogs at each time. An ANCOVA controlled for pretreatment values of variables was performed to detect differences in posttreatment values for variables between small (< 5-kg) and large (> 5-kg) dogs and between male and female dogs. Statistical analyses of IOP, TBUT, CTT, pupil diameter, and STT-1 were performed with software.[e] Values of $P \leq 0.05$ were considered significant.

Results

Twelve dogs were included in the study. Breeds included Golden Retriever (n = 3), Labrador Retriever (2), Basset Hound (1), Brussels Griffon (1), long-haired Chihuahua (1), Old English Sheepdog (1), Poodle mix (1), and Staffordshire Bull Terrier mix (1). Four of the dogs were spayed females, and 8 were neutered males. Three of the dogs were small (weight, < 5 kg) and 9 were large (weight, ≥ 5 kg). Ages of dogs ranged from 2 to 9 years.

For each dog, mean pupil diameters of each (right and left) eye on days 1 through 5 were compared. No significant relationship between day and right pupil diameter was detected for 10 of the 12 dogs. Right pupil diameters slightly decreased during days 1 through 5 for 2 of the dogs (Spearman $\rho = 0.764$ [$P = 0.046$] and Spearman $\rho = 0.793$ [$P = 0.033$]). No significant relationship between day and pupil diameter was detected for the left eye of any of the dogs.

For each dog, mean IOP of each (right and left) eye on days 1 through 5 was compared. No significant relationship between day and IOP of the right eye was detected for any of the dogs in the study. No significant relationship between day and IOP of the left eye was detected for 11 of the 12 dogs. The IOP of the left eye of one of the dogs decreased significantly (Spearman $\rho = 0.857$ [$P = 0.014$]) during days 1 through 5.

The GCD values in conjunctival biopsy samples obtained on day 1 (before treatment with diphenhydramine) ranged from 6 to 41 goblet cells/100 epithelial cells (mean, 17.46 goblet cells/100 epithelial cells). The GCD values in conjunctival biopsy samples obtained on day 21 (after treatment with diphenhydramine) ranged from 8 to 36 goblet cells/100 epithelial cells (mean, 17.17 goblet cells/100 epithelial cells). No significant differences were detected between conjunctival GCD values for days 1 and 21.

Results of a paired samples *t* test (12 degrees of freedom) indicated mean ± SD pretreatment (day 1) TBUT values (15.21 ± 6.38 seconds) were significantly ($P = 0.008$) higher than posttreatment (day 21) TBUT values (8.08 ± 3.43 seconds; **Table 1**). Corneal esthesiometry values were evaluated via that same statistical method; results indicated pretreatment CTT values (3.77 ± 0.76 mg/0.0113 mm^2) were significantly ($P < 0.001$) higher than posttreatment CTT values (2.42 ± 0.88 mg/0.0113mm^2). No significant differences were detected between pretreatment and posttreatment STT values for either eye. No significant differences were detected for values of any of the variables between large versus small dogs or between female versus male dogs.

Discussion

Hydroxyzine and diphenhydramine are first-generation antihistamines that are commonly administered orally to dogs for treatment of atopic dermatitis and other types of allergic dermatitis.[7,11] The anticholinergic activity of these drugs may cause an increase in IOP via pharmacologically induced mydriasis because pupillary dilation may impair outflow of aqueous humor at the iridocorneal angle. Because of the anticholinergic activity of this drug, other authors[12] have recommended that hydroxyzine be used with caution in humans predisposed to glaucoma or undergoing treatment for glaucoma. Caution is recommended[8,13] for oral administration of diphenhydramine to humans with open- or closed-angle glaucoma. To the authors' knowledge, administration of hydroxyzine to humans or dogs has not been reported to decrease tear production or increase pupil diameter. However, administration of cetirizine (the major metabolite of hydroxyzine) to humans decreases tear production and tear film quality (as determined via decreased TBUT).[4,6] To the authors' knowledge, the effects of diphenhydramine administration on tear production in humans have not been investigated. Results of a recent study[14] indicated short-term oral administration of diphenhydramine did not have an effect on aqueous tear production of clinically normal dogs. Results of the present study that STT values for dogs were similar before and after oral administration of diphenhydramine for 21 days supported results of that other study.[14] However, TBUT and CTT values for dogs decreased during the present study, indicating diphenhydramine administration to dogs decreased tear film stability and corneal sensitivity, respectively. Clinically important adverse effects of diphenhydramine administration were not detected in dogs in this study. A significant decrease in pupil diameter was detected for 1 eye in each of 2 dogs during treatment with diphenhydramine in this study, although the decrease was small in comparison with baseline values. Also, IOP was within the reference range (15 to 25 mm Hg) for the dog that had a significant decrease in IOP during the study.[2] These differences in data among dogs could be attributed to investigator error during measurements, difficulty in obtaining measurements because of inad-

Table 1—Values of various ophthalmologic variables for 12 clinically normal dogs before (pretreatment) and after (posttreatment) oral administration of diphenhydramine for 21 days.

Variable	Mean	Range	SD
TBUT(s)*			
Pretreatment	15.21	7.0–26.0	6.38
Posttreatment	8.08	3.0–18.0	3.43
CTT (mg/0.0113 mm^2)*			
Pretreatment	3.77	2.0–5.5	0.76
Posttreatment	2.42	1.0–4.0	0.88
STT-1 (mm of wetting/min)			
Pretreatment	22.63	19.0–30.0	3.44
Posttreatment	23.08	15.0–29.0	2.32

*Pretreatment and posttreatment values are significantly ($P \leq 0.008$ for all comparisons) different.

equate cooperation of dogs, or variability among dogs regarding these variables. Because pupil diameters and IOPs were within reference ranges (compared with the other clinically normal dogs in the study), we did not conclude that diphenhydramine administration to dogs should be avoided.

Results of this study indicated conjunctival GCDs did not change during oral administration of diphenhydramine to dogs for 21 days. Interestingly, TBUT for dogs decreased during the study; this finding would typically be attributed to a decrease in the number of goblet cells. Measurement of tear mucin could have been performed to further investigate the amount and function of preocular gel mucin of dogs. However, conjunctival GCD is the most sensitive indicator of the health of ocular surfaces.[9] Chronic conjunctival inflammation can cause squamous metaplasia and loss of goblet cells, but some types of chronic inflammation (including allergies) can cause an increase in conjunctival GCD.[15,16] In the present study, goblet cells were counted in an area that was considered representative for each conjunctival biopsy sample slide (as determined by the board-certified veterinary pathologist). This method may have affected mean values, so results may not be representative of changes in TBUT that develop clinically in dogs. Conjunctival biopsy samples were obtained from the lower nasal conjunctival fornix of each eye of dogs in this study because that location has one of the highest GCDs in dogs.[9] However, GCDs may differ among conjunctival areas, and goblet cells in different conjunctival areas may not respond to damage or injury in the same manner.[14]

Results of the present study indicated corneal sensitivity of dogs decreased during treatment with diphenhydramine. These results were difficult to explain. One explanation for this finding was that determination of corneal esthesiometer measurements was subjective and required cooperation of dogs. No significant differences were detected between corneal sensitivities of male versus female dogs or between large versus small dogs.

Some breeds of dogs are predisposed to concurrent development of skin and ophthalmic diseases. Therefore, results of this study may be particularly relevant for American Cocker Spaniels (predisposed to KCS and primary glaucoma), English Bulldogs (predisposed to KCS), and Basset Hounds (predisposed to primary glaucoma), among others.[2]

Results of this study suggested that diphenhydramine can be administered orally to clinically normal dogs for 21 days without development of clinically relevant changes in values of ophthalmologic variables. These findings suggested administration of diphenhydramine to clinically normal dogs would not likely cause glaucoma or KCS. However, results of this study did not indicate the safety of orally administered diphenhydramine in dogs with KCS or primary glaucoma or in dogs genetically predisposed to these conditions. The dogs included in this study had gonioscopically normal eyes; therefore, conclusions cannot be made regarding safety of diphenhydramine in dogs genetically predisposed to primary glaucoma. Caution is advised regarding oral use of antihistamines (including diphenhydramine) in human patients receiving treatments for glaucoma because drug-induced mydriasis may cause an increase in IOP.[1,3] Further investigation is warranted to determine whether administration of diphenhydramine to dogs with glaucoma or gonioscopically abnormal eyes causes an increase in pupil diameter, which may potentiate glaucoma. Similarly, the effects of orally administered diphenhydramine on tear production of dogs with KCS should be determined before recommendations can be made regarding routine administration of diphenhydramine to such dogs. Future studies are also warranted in which the effects of topically administered antihistamines on ophthalmologic variables are determined.

a. Cochet and Bonnet aesthesiometer, Luneau Ophtalmologie, Chartres Cedex, France.
b. TonoVet, Jorgensen Laboratories, Loveland, Colo.
c. Diphenhydramine hydrochloride, 25 mg, Target Brands Inc, Minneapolis, Minn.
d. Proparacaine hydrochloride ophthalmic solution USP, 0.5%, Bausch & Lomb Inc, Tampa, Fla.
e. SPSS, version 19.0, IBM Corp, Armonk, NY.

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