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Effects of topical administration of 1% brinzolamide on normal cat eyes

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Abstract

Objective To evaluate the effect of short-term daily topical administration of 1% brinzolamide on the intraocular pressure (IOP) of healthy domestic cats with normotensive eyes and to assess the potential for negative side effects of drug administration.

Animals Twelve privately owned adult domestic cats without physical or ocular abnormalities.

Procedure Normal variation in IOP was determined on day 1. Cats were then treated on days 2–8 with a topical placebo (artificial tear solution) OU q 12 h. On days 9–15 the cats were treated q 12 h with 1% brinzolamide in one randomly selected eye and the placebo in the contralateral eye. All medications (drug and placebo) were administered twice daily at 7 a.m. and 7 p.m. On days 16–22 the cats received no topical medications. IOP, horizontal pupil size in mm and assessment of conjunctival hyperemia were noted OU on days 1, 8, 15 and 22 at 5 time points (9 a.m., 11 a.m., 1 p.m., 3 p.m. and 5 p.m.). Mixed linear regression models were used to compare the IOP of each eye at all time periods for each cat, controlling for age and weight.

Results Mean IOP was not significantly altered in any eye at any time point during the treatment period compared with pretreatment, baseline, or follow-up evaluations. Conjunctival hyperemia and miosis were not detected in either eye at any time point.

Conclusions and clinical relevance Short-term q 12 h administration of 1% brinzolamide did not significantly reduce IOP in this small sample population of normotensive cats under these study conditions. No clinically relevant side effects were noted with brinzolamide administration.

Key Words: brinzolamide, carbonic anhydrase inhibitor, cats, glaucoma, intraocular pressure

INTRODUCTION

Glaucoma is a leading cause of blindness in animals and may be classified as primary or secondary. Primary glaucoma is uncommon in cats and occurs with no antecedent ocular disease.[1–5] In cats, glaucoma usually occurs as a sequelae to chronic uveitis caused by infectious disease (FIV, FeLV, FIP, toxoplasmosis, bartonellosis), neoplasia, and idiopathic or immune-mediated disease.[1–5]

Despite improvements in surgical intervention, medical therapy has been and remains a mainstay in the treatment of glaucoma in veterinary medicine. A recent review suggested that the most common antiglaucoma medication used to treat feline glaucoma is 0.5% timolol maleate,[1] a beta-adrenergic blocker. Due to the small body size of cats, as well as the frequent occurrence of uveitis and secondary glaucoma in older cats that may have cardiopulmonary compromise (i.e. feline asthma, cardiomyopathy, hypertension, hyperthyroidism), administration of a B-adrenergic blocker could lead to systemic, life threatening side effects.[6] In a recent abstract 2% dorzolamide has been shown to significantly decrease the IOP in normotensive cats.[7] Therefore, exploring safer alternatives for treatment of feline glaucoma is warranted.

Carbonic anhydrase inhibitors (CAI) encompass a group of medications that have been commonly used for glaucoma management in a variety of species. Carbonic anhydrase (CA) is an endogenous enzyme present in several tissues of the body including the pigmented and nonpigmented ciliary body epithelium, red blood cells, and kidney nephrons. CA catalyzes the reaction involving the hydration of CO_2 and

the dehydration of carbonic acid. HCO_2^- and H^+ formed in epithelial cells are exchanged for Cl^- and Na^+, respectively. The net movement of Cl^- and Na^+, through gap junctions in nonpigmented epithelial (NPE) cells and the $Na^+/K^+/2Cl^-$ cotransporter, into the aqueous is accompanied by water.[8–10] The result is a constant rate of aqueous humor production or flow (AHF).

It has been reported that patients with glaucoma have a normal AHF rate[11,12] and CAI are known to decrease IOP exclusively by reducing this rate.[13–15] This occurs in the ciliary processes of the eye through the inhibition of CA, which disrupts the formation of bicarbonate ions and subsequently impedes Na^+ and fluid transport.[16]

Because CA is present in other body tissues, CAI are not selective for the uveal tract and systemic administration of CAI carries a significant risk of side effects. These include metabolic acidosis, general malaise, fatigue, depression, hyperkalemia, blood dyscrasis, anorexia, gastrointestinal disturbances (i.e. nausea, vomiting, diarrhea), weight loss, urologic signs (i.e. urolithiasis, hyperuricemia, anuria), teratogenesis and paresthesis.[17,18] Adverse systemic effects have necessitated the termination of therapy in up to 50% of humans.[17] Depression, anorexia, vomiting and diarrhea are the most common side effects reported in dogs.[13,19,20]

Several topical CAI have been developed in an attempt to provide the ocular benefits of CAI without the complications associated with systemic administration.[21] These topical CAI agents have proven as effective as systemic CAI in humans.[14,22–26] Topical CAI have also been shown to significantly lower IOP in dogs,[13,27,28] rabbits,[29,30] horses[31] and monkeys.[15] Side effects of topical CAI administration include: ocular stinging and burning, ocular discharge, keratitis, conjunctival hyperemia, blepharitis, dry eye, blurred vision, ocular pruritis, foreign body sensations, taste aversion, dermatitis, headache and rhinitis. Despite the widespread use of topical CAI in clinical veterinary medicine, they have not been studied extensively in cats.

Dorzolamide hydrochloride [(4S-*trans*)-4-lethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride] was the first topical CAI developed for the treatment of glaucoma in humans.[21] In humans[25] and dogs[13] it is recommended q 8 h for greatest results. In horses dorzolamide provides no significant decrease in IOP with short-term q 24 h dosing; however, it may significantly decrease IOP in horses with q 12 h therapy.[31]

Brinzolamide (Azopt®, Alcon Laboratories Inc., Fort Worth, Texas, USA) [R-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide] is another topical sulfonamide-based medication for the treatment of glaucoma in humans.[32] Brinzolamide is as effective as dorzolamide in decreasing IOP with only q 12 h therapy in humans[22] and appears to have fewer side effects compared to dorzolamide, including less ocular discomfort on administration.[25,33,34] This is probably because of its optimized suspension formulation at physiologic pH (7.5) (vs. dorzolamide (5.6)).[32,35]

The purpose of this study was to determine the efficacy of 1% brinzolamide in lowering IOP in normotensive cats, and to document any negative side effects of topical administration.

MATERIALS AND METHODS

Animals

Twelve healthy privately owned adult cats of both sexes (eight male, four female) comprised the study population. Cats were selected on the basis of a normal physical and ocular examination as determined by Schirmer tear test (STT) (Schirmer tear test strips, Schering-Plough Animal Health Corp., Union, New Jersey), fluorescein staining (Fluorets, Chauvin Pharmaceuticals Ltd, Harold Hill, Romford, Essex, UK), applanation tonometry (Tono-Pen® XL, Mentor Ophthalmics, Norwell, MA, USA), biomicroscopy (SL-14 Kowa, Kowa Company Ltd, Japan), and indirect ophthalmoloscopy (Heine Omega 200, Heine Optotechnik, Herrsching, Germany). Four different breeds were represented (six DLH, three DSH, two Siamese, one Cornish Rex). Cats ranged in age from 2 years to 14 years (mean 6.5 years). Their weight varied from 2.8 to 7.5 kg (mean 5.96 kg).

Parameters measured

Intraocular pressure, horizontal pupil size and conjunctival hyperemia were assessed OU on days 1, 8, 15 and 22 of the study at 9 a.m., 11 a.m., 1 p.m., 3 p.m. and 5 p.m. The same observer (HEG) performed all measurements. A single applanation tonometer was used consistently throughout the experiment in accordance with the manufacturer's recommendations. The cats were manually restrained and 1 drop of topical anesthetic (Alcaine, Alcon Laboratories Inc.) was applied to each eye immediately prior to tonometry. The head was maintained in a normal, upright position during measurements. Recorded IOP was an average of three consecutive tonometry readings with an error of ≤ 5%. Pupil size was measured in uniform illumination on the horizontal axis in the center of the pupil, using a millimeter ruler, positioned just anterior to the cornea. Conjunctival hyperemia was recorded using a scale of 0 to 3 (none = 0; mild = 1; moderate = 2; severe = 3).

Drug administration

Pre-treatment IOP was determined on day 1 of the study. The cats were then treated by their owners at home on days 2–8 with topical artificial tear solution (Tears Naturale®, Alcon Labratories Inc.) (placebo) OU q 12 h, in order to acclimatize them to eye drops. On days 9–15 the cats were treated q 12 h with 1% brinzolamide in a randomly selected eye and the placebo in the contralateral eye. Medications were administered twice daily at 7 a.m. and 7 p.m.. On days 16–22 the cats received no topical medications. Cats were brought to RMAH on days 1, 8, 15 and 22, and IOP, pupil size and conjunctival hyperemia were assessed at 5 time points (9 a.m., 11 a.m., 1 p.m., 3 p.m. and 5 p.m.).

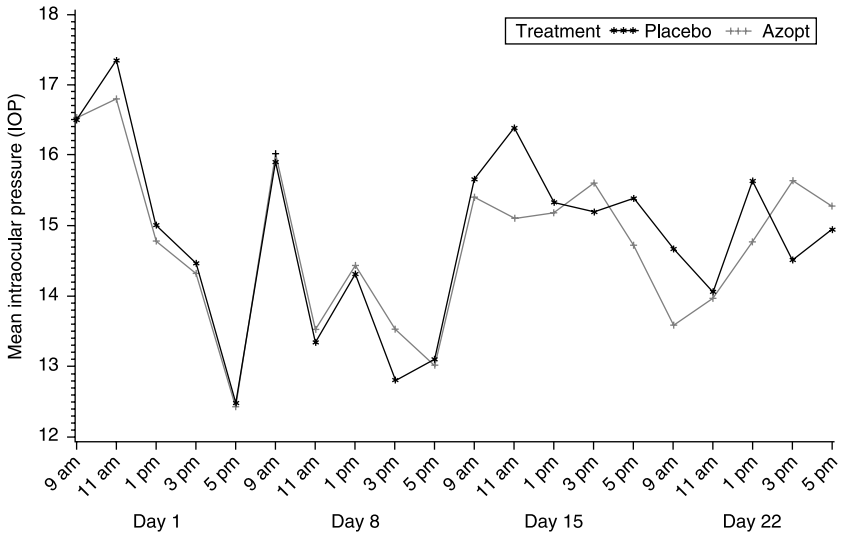

Figure 1. Graph depicting mean intraocular pressure (IOP) over time for 12 cats that received topical 1% brinzolamide twice daily. Points represent mean IOP at each time point. Day 1 represents pre-treatment values, day 8 the baseline, day 15 the treatment period, and day 22 the follow-up monitoring period.

Data analysis

The IOP used for analysis was the mean of the three tonometric readings for that eye. Mixed linear regression models were used to compare IOP of each eye (treated and control), at each time period (pretreatment, baseline, treatment period and follow-up) for each cat, controlling for the weight and age of the animal, with the equation:

$$Y_{ij} = (\beta_{0j} + b_i) + \beta_{1j} \times \text{TREATMENT} + \beta_{2j} \times \text{TIME} + \beta_{3j} \times \text{AGE} + \beta_{4j} \times \text{WEIGHT} + \varepsilon_{ij}$$

In this equation, β_{0j} is the intercept of this regression line for the jth time period (j = pretreatment, 1 = baseline period, 2 = treatment period, and 3 = follow-up); β_{1j} is the average difference in IOP between treated and control eyes for the jth time period; β_{2j} is the slope of the regression line over the course of the day for the jth period, where the slope is an estimate of the average change in IOP for each 1-h change in time; β_{3j} is an estimate of the average change in IOP for each 1-year increase in the age of a cat; and β_{4j} is an estimate of the average change in IOP for each 1 pound increase in the weight of a cat; b_i and ε_i are normally distributed random variables where i designates the cat (i = 1–12).

Regression lines were generated separately for each group and time period, and interactions between the variables were tested. One overall regression line, combining all of the time periods, was computed to assess the differences between baseline, treatment and follow-up (while controlling for eye, age and weight), and to investigate interactions.

The mean IOP and standard deviation were calculated for each eye (treated or control) for the 4 different time periods (averaging the five measurements per day). A plot of the mean values over time was created. Values of $P < 0.05$ were considered significant. One overall model was fit to assess the differences in IOP between the different treatment days, controlling for treatment received as well as age and weight. This model uses day 1 as the reference group; estimated coefficients in the model indicate the average difference between the other days from day 1.

RESULTS

Analysis of the mixed linear regression models indicated that there was no significant difference in IOP between the treated and placebo eyes. No significant effect of age or weight was detected at any time period.

Mean (± SEM) overall pretreatment IOP was 15.16 ± 3.68 mmHg in the eye subsequently administered placebo, and 14.97 ± 3.65 mmHg in the eye subsequently treated with brinzolamide. Mean (± SEM) baseline IOP (prior to initiating brinzolamide) was 13.89 ± 2.95 mmHg (placebo) and 14.11 ± 3.00 mmHg (brinzolamide). Mean IOP following the treatment period was 15.59 ± 2.64 mmHg in the placebo eye and 15.12 ± 2.84 mmHg in the brinzolamide-treated eye. Mean IOP at follow-up was 14.76 ± 2.40 mmHg in the eye previously treated with placebo and 14.65 ± 2.51 mmHg in the eye previously treated with brinzolamide. There were no significant differences between the treatment and placebo eyes.

Analysis of the mixed linear regression results indicated that mean IOP was not significantly changed at any time during the study period. Values for overall mean IOP for each time point were plotted (Fig. 1). Daily values of IOP varied, without a readily definable pattern.

The overall model results are shown in Table 1. Although a trend toward reduced IOP in the brinzolamide-treated eye was identified in several cats, when data were averaged over time, cat and eye, the results were not statistically significant ($P = 0.4462$). Weight differences did not affect IOP ($P = 0.5801$). The model results suggest that the mean IOP decreases by 0.20 for every year increase in age, after controlling for treatment, time, day and weight of the cat. This change was statistically significant ($P = 0.0049$). Pupil size was not significantly different in the treated and placebo eyes

Table 1. Results of a mixed linear regression model that compared IOP in 12 cats treated with topical 1% brinzolamide q 12 h. IOP was measured prior to entry into the study (pretreatment), following placebo administration only (baseline), during treatment and after treatment (follow-up monitoring)

Variable		Estimate/coefficient	*P*-value	95% confidence limits	
Treatment		–0.13	0.4462	–0.49	0.23
Day 8: Placebo	8	–1.19	0.0007	–1.89	–0.50
Day 15: Brinzolamide	15	0.17		–0.61	0.95
Day 22: No treatment	22	–0.44		–1.16	0.29
Time		–0.18	0.0113	–0.31	–0.04
Age		–0.20	0.0049	–0.33	–0.08
Weight		0.05	0.5801	–0.13	0.23
Day × time interaction	8	0.28	< 0.0001	0.05	0.51
	15	0.55		0.29	0.81
	22	0.77		0.51	1.03

at any time point, and conjunctival hyperemia did not occur at any time in the study.

DISCUSSION

Brinzolamide was chosen for this study because it is as effective as dorzolamide in decreasing IOP with only q 12 h topical therapy in humans[22,25] and dogs,[28] and has fewer side effects.[25,36–38] Short-term administration of brinzolamide q 12 h did not reduce mean IOP from baseline values in treated or control eyes in this population of normotensive cats.

There are several possible reasons why 1% brinzolamide did not significantly reduce IOP in this study. As a trend toward reduced IOP in the brinzolamide-treated eye was identified in several cats, a larger number of test subjects may have shown a statistically significant difference. Secondly, poor compliance or medication technique by the owners could contribute to a failure to detect differences in IOP with brinzolamide therapy. A questionnaire was given to the cats' owners at the end of the study to determine compliance. Questionnaire response suggested good compliance. Thirdly, drug concentration and frequency of administration are additional factors to consider when employing a drug in different species. For example, in humans there is a significant difference in efficacy between 0.3% and 1% brinzolamide, but no significant difference in efficacy between 1%, 2%, and 3% brinzolamide.[36] The incidence of associated side effects are also dose-dependent.[36] The 1% concentration is the only commercially available product. Clinically, 1% brinzolamide significantly decreases the IOP from baseline in humans[22,25,36] and dogs.[28] It is possible that a higher concentration is required to be effective in cats. Studies performed in glaucomatous humans revealed that q 12 h brinzolamide therapy was as effective as q 8 h therapy,[25,35,39] and either frequency was as effective as 2% dorzolamide q 8 h.[25,35,39] One study did report that in glaucomatous humans brinzolamide q 8 h reduces the IOP by > 5 mmHg or decreases the IOP to < 21 mmHg in 80.1% of subjects whereas only 75.7% are similarly affected with q 12 h therapy.[25] This indicates that there is a subpopulation of humans who would benefit from q 8 h administration. In an initial canine study q 12 h brinzolamide therapy significantly reduced the IOP in normotensive dogs[28] with the peak effect on IOP seen at $5^1/_2$ to 6 h post medication. Intraocular pressures returned to pretreatment values by 10.5 h post therapy, suggesting that q 8 h treatment may be more appropriate.[28] It is possible that a q 12 h therapy is not sufficient in cats either, or that brinzolamide does not significantly decrease IOP in cats with normotensive eyes regardless of concentration or dose frequency. This may be related to the high rate of AHF in the cat (14.4 ± 0.9 μL/min)[40] when compared to that of dogs (4.5–5.5 μL/min)[41] and humans (1–3 μL/min).[8] In humans treated with brinzolamide, the AHF rate is decreased by 0.2–0.5 μL/min,[22] an overall reduction in aqueous production of 16–19%. A similar decrease of 0.5 μL/min in cats would result in a relatively smaller decrease in AHF rate of 3.6%, perhaps reducing the efficacy of CAI in this species. The theory of a relatively smaller decrease in AHF needs to be explored further.

There is a tendency for certain antiglaucoma medications to have a greater hypotensive effect on eyes with glaucoma vs. normal eyes.[19,42,43] In normotensive humans brinzolamide decreases IOP by approximately 1.5 ± 1.1 mmHg at night and 0.3 ± 1.6 mmHg in the morning,[22] whereas a 3.4–5.7 mmHg decrease occurs in glaucomatous eyes.[25,34] We are therefore unable to extrapolate our findings in normotensive cats and are unable to rule out an improved response to 1% brinzolamide in glaucomatous cats.

The significant decrease in IOP as cats age has been reported previously.[44–46] A more recent study in 100 cats suggested that IOP does not vary significantly with age.[47] In humans there is a reduction in aqueous production and a decrease in uveoscleral outflow with age.[48] The result is a mean intraocular pressure that does not change.[48] The reason for the decrease in IOP in cats in our study remains speculative.

In conclusion, short-term topical administration of 1% brinzolamide did not significantly reduce mean IOP from pretreatment levels in this small sample population of

normotensive cats. Further studies to define the therapeutic efficacy of 1% brinzolamide in glaucomatous cats are required.

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