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Moro Bassil Dower, Nathalie; do Espirito Santo Maciel, Camila; Spiller, Paulo Roberto;  
Dumit Pizzinatto, Fábio; Ghisi Gomes, Lianna; Ito Yamauchi, Kelly Cristiane; Alaião  
Gonçalves, Lucas; Pinto Ribeiro, Alexandre

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## Effects of 1% Topical Brinzolamide on Intraocular Pressure in Healthy Dogs

Nathalie Moro Bassil Dower<sup>1</sup>, Camila do Espirito Santo Maciel<sup>1</sup>, Paulo Roberto Spiller<sup>1</sup>,  
Fábio Dumit Pizzinatto<sup>1</sup>, Lianna Ghisi Gomes<sup>1</sup>, Kelly Cristiane Ito Yamauchi<sup>2</sup>,  
Lucas Alaião Gonçalves<sup>2</sup> & Alexandre Pinto Ribeiro<sup>1</sup>

### ABSTRACT

**Background:** Glaucoma is one of the most common causes of blindness in dogs, and is generally characterized by death of the retinal ganglion cells associated with a rapid loss of vision. Increased intraocular pressure (IOP) occurs in patients with primary glaucoma, due to genetic abnormalities in pectinal ligaments and the trabeculae of the iridocorneal angle, producing inadequate drainage of aqueous humor. IOP is the result of the dynamic equilibrium between the production and drainage of aqueous humor. Intraocular surgery, anterior lens luxation, systemic diseases, immune-mediated, neoplastic and infectious diseases lead to the breakdown of the blood-aqueous barrier and increase the amount of protein and cells in aqueous humor, which can block this drainage pathway. Under these conditions, becomes indispensable the pharmacological control of IOP by reducing aqueous humor production. The main objective of the present study was to evaluate the effects of topical 1% brinzolamide on intraocular pressure (IOP) in twelve healthy dogs.

**Materials, Methods & Results:** The age range of affected dogs was 1-5 years, with a mean age of 2.5 years. Twelve dogs were included in this study. All animals were healthy based on clinical, ophthalmic and hematological examinations. Selected animals were kept in a room with 500 lux luminosity, 56.8% relative humidity, 20°C temperature, exposed to 12 h of light/dark cycle, were fed twice daily and water *ad libitum*. All animals were adaptation to the procedures and examiners and IOP was measured by applanation tonometry at 08:00 a.m., 11:00 a.m., 02:00 p.m., 05:00 p.m., and 08:00 p.m., for 7 days and 2 days of baseline. Subsequently, one eye of each dog was randomly assigned, the eye received one drop of 1% brinzolamide at 08:30 a.m., 02:30 p.m., and 08:30 p.m. during four consecutive days and adelfo eyes received one drop of sterile saline solution and were considered control eyes. During the treatment phase and on the day after the treatment had finished, all parameters were evaluated in a blind fashion at the same pre-established time points. The value for IOP during the baseline of the treated eye were  $16.77 \pm 0.22$  mmHg. The baseline period, values did not differ significantly between treated and control eyes. Comparison between the first day of brinzolamide-treated eyes with the average daily values of the two days of the baseline period showed that IOP decreased significantly 8.88%. IOP after four days of daily instillations of brinzolamide was able to decrease overall IOP by 1.42 mmHg (8.47%) when compared with the baseline period. Overall IOP values in the brinzolamide-treated eyes decreased 1.02 mmHg (6.24%) when compared to the control eyes. There were no statistically significant differences when compared control eye to baseline. Three times daily instillations of 1% brinzolamide in healthy dogs significantly decrease 8.47% IOP. During the post-treatment period, the average daily values of the brinzolamide-treated eyes remained 1.52 mmHg below the average daily values observed at baseline period.

**Discussion:** The present research showed that, the average daily IOP values in the brinzolamide-treated eyes decreased 1.49 mmHg (8.88%) at the end of the first day, 1.69 mmHg (10.07%) at the end of the fourth day, and the cumulative IOP values after four days of treatment, were able to decrease by 1.42 mmHg (8.53%). Three times daily instillations of 1% brinzolamide in healthy dogs significantly decrease IOP, and therefore may be indicated to management of intraocular hypertension and glaucoma.

**Keywords:** carbonic anhydrase inhibitors, ocular hypertension, intraocular pressure, glaucoma.

## INTRODUCTION

Primary glaucoma may result from abnormal biochemical metabolism of the trabecular cells of the outflow system or the physical effects of pupillary blockage and changes in the iridocorneal angle, which leads to inadequate aqueous humor drainage elevated intraocular pressure (IOP). Intraocular surgeries, anterior lens luxation, neoplastic, immune-mediated, and infectious diseases lead to the breakdown of the blood-aqueous barrier, increasing the influx of proteins and cells into the aqueous humor. Such conditions have the potential to increase and even sustain elevated IOP values [5].

Brinzolamide is a carbonic anhydrase inhibitor (CAI) that reduces the activity of carbonic anhydrase II secreted by non-pigmented ciliary epithelial cells. Thus, the osmotic gradient decreases and, consequently, so does the aqueous humor production and the IOP [9].

In the only study carried out on dogs with brinzolamide, average daily IOP value was not described, being reported only the lowest and highest IOP value after a single instillation; and the drug action was assessed for only 10.5 h [8]. One should consider that longer periods of evaluation may be necessary to conclude the time point in which the drug reaches its maximum effect on IOP. Comparisons between brinzolamide and dorzolamide in man showed that the former had a significantly higher tolerability than the later drug, probably because of having more neutral pH [6,7].

Considering that the hypotensive effects of brinzolamide are similar to dorzolamide in dogs, and greater inhibitory potential on carbonic anhydrase II [3], than dorzolamide, the present study aimed to assess the effects of 1% brinzolamide over the IOP in healthy dogs.

## MATERIALS AND METHODS

### *Animals*

Breeds enrolled included Shih-Tzu ( $n = 2$ ), Poodle ( $n = 4$ ), and Yorkshires ( $n = 6$ ), with average age and weight of 2.5 years (between 1 and 5 years) and 3.18 kg (between 1.8 kg and 6.3 kg), respectively. Dogs were selected if no abnormalities were detected after a full clinical, ophthalmic, and hematological exam. Selected animals were kept in a room with 500 lux luminosity, 56.8% relative humidity, 20°C temperature, Multifunction Meter ITMP-600 Medidor Multifunção ITMP-600 Instrutemp<sup>1</sup>, exposed to 12 h of light/dark

cycle, were fed with a dog dry pellet twice daily, and provided with water *ad libitum*.

### *Experimental Design*

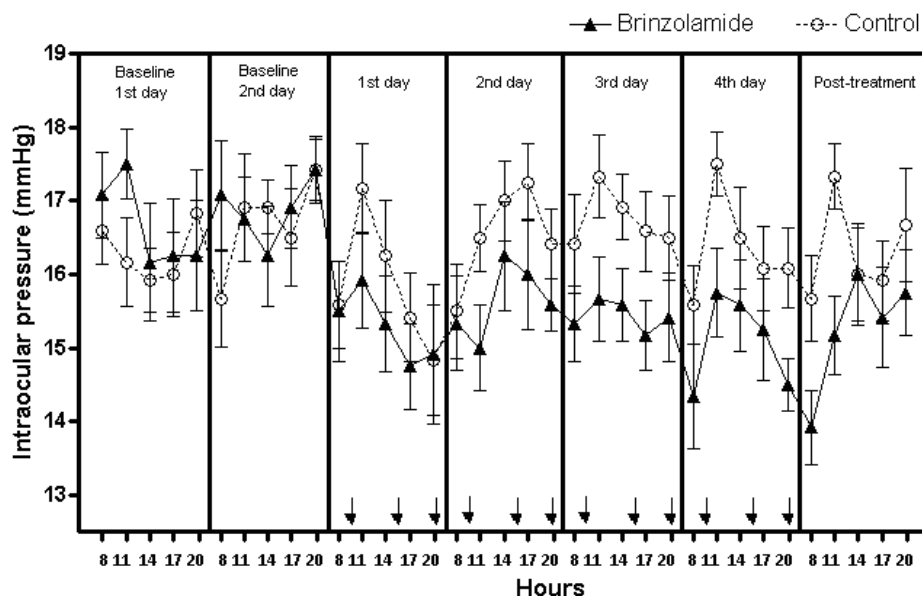
In order to acclimate the dogs to the procedures and examiners, physical restraint was used and IOP was measured by means of applanation tonometer, Tono-Pen<sup>®</sup> XL<sup>2</sup>, for seven consecutive days at 08:00 a.m., 11:00 a.m., 02:00 p.m., 05:00 p.m., and 08:00 p.m. Following the acclimation period of seven days, the parameters were assessed for two consecutive days at the same time points aforementioned to establish baseline IOP values. On the next day, one eye of each dog was randomly assigned and treated for four consecutive days with one drop of 1% brinzolamide (Azopt)<sup>3</sup> at 08:30 a.m., 02:30 p.m., and 08:30 p.m. The fellow eyes received one drop of sterile saline solution and were used as control. During the treatment phase and on the day after the treatment had finished, all parameters were evaluated in a blind fashion at the same pre-established time points.

### *Statistical Analysis*

One-way analysis of variance for repeated measures followed by the multiple comparisons Newman-Keuls test (PRISM 4.0<sup>®</sup>)<sup>4</sup> were used to assess the main effects of treatment and time, as well as their interaction in and between the control and treated eyes. The values of IOP in the control and treated eyes were compared during the baseline period. Average daily IOP values of the treated and control eyes assessed on the two days of the baseline period were compared to the average daily values of the treated and control eyes assessed during each day of the treatment and post-treatment periods. The average daily IOP values of the treated and control eyes were also compared among the treatment days. In all occasions, values of  $P < 0.05$  were considered significant.

## RESULTS

The results were presented as means  $\pm$  standard error of the means (SEM). The values for Intraocular Pressure (IOP) during the baseline, treatment, and post-treatment periods are shown in Figure 1. At the end of the baseline period, the mean values of the treated and control eyes were  $16.77 \pm 0.22$  and  $16.49 \pm 0.18$  mmHg, respectively. Throughout the baseline period, values did not differ significantly between treated and control eyes ( $P = 0.3607$ ).



**Figure 1.** Mean  $\pm$  SEM of intraocular pressure (mmHg) during 2 days of baseline periods and following topical 1% brinzolamide (arrows) at 08:30 a.m., 02:30 p.m., and 08:30 p.m. during the four days of the treatment, and post-treatment periods in clinically healthy dogs.

Comparisons between the average daily values of brinzolamide-treated eyes with the average daily values of the two days of the baseline period showed that IOP decreased significantly ( $P < 0.001$ ) by 1.49 mmHg (8.88%), 1.14 mmHg (6.79%), 1.34 mmHg (7.99%), and 1.69 mmHg (10.07%) from the first to the fourth day of treatment period. During the same period, the control eyes did not differ significantly when compared to the baseline period ( $P = 0.0578$ ). Comparisons of the average daily IOP values among the four days of treatment did not differ significantly in the treated eyes ( $P = 0.3705$ ). The same comparisons for the control eyes showed a significant IOP reduction of 0.90 mmHg between the first and the third day of the treatment phase ( $P < 0.05$ ). During the treatment period, the highest and lowest IOP values observed were 20 and 12 mmHg in the control eyes and 20 and 10 mmHg in the treated eyes.

In the comparisons between the average daily values of the brinzolamide-treated eyes and the average daily values of the control eyes, IOP decreased 0.56 mmHg in the first day in the eyes receiving brinzolamide; however, such reduction was not significant ( $P > 0.05$ ). In the second [-0.90 mmHg] ( $P < 0.05$ ), third [-1.31 mmHg] ( $P < 0.01$ ), and fourth [-1.26 mmHg] ( $P < 0.01$ ) days of treatment such parameter decreased significantly in the eyes receiving brinzolamide.

During the post-treatment period, the average daily values of the brinzolamide-treated eyes remained

1.52 mmHg below the average daily values observed at baseline period ( $P < 0.001$ ). During the same period, the average daily values of the control eyes did not differ significantly when compared to the baseline period ( $P = 0.4456$ ).

## DISCUSSION

The present research showed that, the cumulative IOP values after four days of daily instillations of 1% brinzolamide three times a day were able to decrease overall IOP by 1.42 mmHg (8.53%) in the treated eye when compared with the baseline period. However, at the end of the treatment period, the mean overall IOP value in the brinzolamide-treated eyes decreased 1.02 mmHg (6.24%) when compared to the control eyes. A previous study showed that the lowest and the highest IOP values recorded 6.5 h following a single instillation of brinzolamide in dogs, were, 3.5 and 8.7 mmHg, respectively [8]. In the present study, the average daily IOP values decreased 1.49 mmHg (8.88%) at the end of the first day of treatment with brinzolamide, and 1.69 mmHg (10.07%) at the end of the fourth day of treatment with brinzolamide. Although these reductions on the IOP were significant when compared to the baseline period, no additive effect was found in the brinzolamide-treated eyes over the four days of treatment. A similar result has been reported in healthy

dogs treated during six consecutive days with 2% dorzolamide [1].

It has been reported that glaucomatous dogs treated twice or three times a day with 2% dorzolamide had lower IOP values in the control eyes [2,4]. In the study of brinzolamide and dorzolamide the authors did not report the effect of IOP untreated eyes [8]. In another study conducted on healthy dogs treated every 8 h with 2% dorzolamide, it was observed that IOP did not decrease in the control eyes [1]. The present results showed that the IOP in the control eyes did not differ when compared to the baseline period.

The same comparisons for the control eyes showed a significant IOP reduction of 0.90 mmHg between the first and the third day of the treatment phase ( $P < 0.05$ ). The reduction of this parameter observed in the control eyes between the first and the third day of the treatment phase may be due to physiological daily fluctuations. It has been reported that reduction of IOP values of the

untreated eye may occur as a result of systemic absorption by part of the agent by the conjunctival vessels [4].

## CONCLUSION

Three times daily instillations of 1% brinzolamide in healthy dogs significantly decrease IOP, and therefore may be indicated to management of intraocular hypertension and glaucoma.

## MANUFACTURERS

<sup>1</sup>Instrumentos de Medição Ltda. São Paulo, SP, Brazil.

<sup>2</sup>Medtronic Solan. Jacksonville, FL, USA.

<sup>3</sup>Alcon Laboratórios do Brasil Ltda. São Paulo, SP, Brazil.

<sup>4</sup>Graphpad software Inc. San Diego, CA, USA.

**Ethical approval.** This study was approved by the institutional Committee for Ethics in the Use of Animals (UFMT) on May 14th, 2015 (protocol 23108.092583/2015-89).

**Declaration of interest.** The authors report no conflicts of interest.

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