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Effects of travoprost 0.004% compared with latanoprost 0.005% on the intraocular pressure of normal dogs

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Abstract

Purpose To compare the effects of travoprost 0.004% and latanoprost 0.005% on the intraocular pressure (IOP) of normal dogs.

Methods Twenty mixed breed dogs were randomized to two groups: latanoprost was used in group A and travoprost in group B. The drugs were instilled in the right eye of the dogs, whereas the left eye received placebo. Both drugs were instilled once a day at 8 AM during 5 days. IOP measurements were made at 8 AM, 10 AM, 2 PM and 8 PM during the 5 days of treatment, the 3 days that preceded treatment, and 3 days following treatment. Presence of blepharospasm, miosis, anterior chamber flare, and conjunctival hyperemia were evaluated during the study.

Results Mean IOP was significantly reduced in the eyes treated with both latanoprost and travoprost, when compared with the eyes treated with placebo ($P < 0.05$). There was no statistically significant difference between the mean IOPs of eyes treated with latanoprost and travoprost at all time intervals during baseline, treatment, and recovery ($P > 0.05$). On the fifth day of treatment and on the first day of the recovery period, a severe ocular hypotension was noted with both drugs, resulting in imprecise readings with the tonometer. Miosis and conjunctival hyperemia were observed in the treated eyes of both groups, whereas flare was noticed in one latanoprost-treated eye.

Conclusion Travoprost 0.004% significantly reduces the IOP in normal dogs. The hypotensive effect obtained with travoprost 0.004% is comparable to that obtained with latanoprost 0.005%.

Key Words: dogs, intraocular pressure, latanoprost, prostaglandin, travoprost

INTRODUCTION

Elevated intraocular pressure (IOP) is the major risk factor for the development of glaucoma. Although improvement on cyclodestructive surgery and aqueous outflow enhancement procedures has given veterinary ophthalmologists better results on the treatment of this disease, medical therapy remains an important strategy to glaucoma control.[1] Prostaglandin analogs represent a class of ocular hypotensive agents that reduce IOP at least as effectively as nonselective β-adrenergic antagonists, and act by increasing uveoscleral outflow.[2,3] Travoprost is an isopropyl ester prodrug that is rapidly hydrolyzed by esterases in the cornea, resulting in travoprost free acid, its biologic active form. In the nanomolar range, the acid has demonstrated preferential affinity and full agonist activity for the FP receptor, with no meaningful affinity for other prostaglandin receptors.[4–6] Latanoprost is a prostaglandin analog and an FP receptor agonist that acts as an ocular hypotensive agent. Latanoprost increases uveoscleral outflow, without affecting aqueous production or conventional drainage.[7–9] Latanoprost is also an ester prodrug and is hydrolyzed by esterases in the cornea, when it becomes latanoprost biologically active acid. The acid is more hydrophilic and is slowly released from the cornea to the aqueous humor for approximately 24 h.[8,10,11] Human and canine ocular tissues have been shown to hydrolyze $PGF_{2\alpha}$ prodrugs in a similar manner.[12] It has been suggested that latanoprost can modify the extracellular matrix in the cillary body by stimulating the activity of metalloproteinases.[13]

Netland *et al.* (2001) compared the effects of travoprost and latanoprost on the IOP of patients with open-angle glaucoma or ocular hypertension. Eight hundred one patients were

randomly distributed to four treatment groups, in an approximate 1:1:1:1 ratio. The efficacy and safety of travoprost 0.0015% and 0.004% instilled at 24-h intervals were compared with latanoprost QD and timolol BID for 12 months. The study suggested that travoprost was superior to timolol and at least as effective as latanoprost in lowering the IOP, and that it was safe and well tolerated in this population.[14]

Studer *et al.* (2000) investigated the effects of latanoprost on the IOP of healthy dogs and cats. The authors concluded that latanoprost significantly reduced the IOP of healthy dogs with no side effects but did not change the IOP of healthy cats.[15] Other studies have suggested that latanoprost and travoprost are effective in lowering the IOP of glaucomatous dogs.[16,17]

However, there are no studies comparing the hypotensive efficacy of travoprost and latanoprost in healthy dogs. The purpose of this study is to compare the hypotensive efficacy and safety of travoprost 0.004% and latanoprost 0.005% in healthy dogs.

MATERIALS AND METHODS

Twenty adult mixed breed dogs were selected (six males) at the veterinary hospital Prof Vicente Borelli of the University of Marilia, Brazil. All dogs were clinically healthy, with a mean weight of 12.25 kg. Before inclusion in the study, the dogs were examined in order to exclude ophthalmic affections that could interfere with the results of this study, such as keratitis, uveitis, and glaucoma. The dogs were examined by slit-lamp biomicroscopy, applanation tonometry, and indirect ophthalmoscopy. Dogs that presented an IOP difference higher than 4 mmHg between the right and left eyes before the beginning of the study were excluded. Animals were kept in kennels, with adequate food and water ad libitum. For this study, the recommendations of the Association for Research in Vision and Ophthalmology (ARVO) for animal research were rigorously followed. The study had the approval of the institution's animal care and use committee.

The dogs were randomized to two groups of 10 animals. The right eye was elected to receive treatment, while the left eye received placebo (Lacrima™, Alcon Laboratories, São Paulo, Brazil). Animals in group A were treated with latanoprost 0.005% (Xalatan™, Pfizer, São Paulo, Brazil), whereas dogs in group B received travoprost 0.004% (Travatan™, Alcon Laboratories, São Paulo, Brazil).

The experiment was divided in three consecutive periods of 3, 5, and 3 days. During the first period, IOPs in both eyes were measured under no medication for the determination of a baseline. During the second period, the right eye of each animal received latanoprost or travoprost, whereas the left eye received placebo. Instillations were always made at 8 AM. During the third period, the drugs were discontinued, and IOPs were measured in order to evaluate recovery.

IOP measurements were made at 8 AM, 10 AM, 2 PM, and 8 PM by the same observer (A.B.C). Applanation tonometry was performed using a tonopen (Tonopen-XL, Mentor Ophthalmics, Norwell, MA, USA). The instrument was calibrated and used according to the manufacturer's specifications. The animals were restrained manually without sedation and one drop of proxymetacaine ophthalmic solution (Anestalcon™, Alcon Laboratories, São Paulo, Brazil) was instilled in each eye before tonometry. Three consecutive valid readings were used to obtain the mean IOP value in each eye at each time interval.

The occurrence of blepharospasm, miosis, and conjunctival hyperemia were also evaluated at 8 AM, 10 AM, 2 PM, and 8 PM. Slit-lamp biomicroscopy was performed at 8 PM to investigate the presence of flare in the anterior chamber.

The comparison between the IOP measurements obtained in the two treatment groups at each time interval was performed using the Student's *t*-test for independent samples. The paired Student's *t*-test was employed to compare the IOPs of treated eyes to baseline values, as well as the IOPs of treated eyes to contralateral eyes that received placebo. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

The mean IOPs of the latanoprost- and travoprost-treated eyes at each time interval are displayed in Tables 1 (baseline), 2 (treatment period), and 3 (recovery). There was no statistically significant difference between the mean IOPs of eyes treated with latanoprost and travoprost at all time intervals during baseline, treatment, and recovery ($P > 0.05$, Student's *t*-test).

Table 1. Mean IOPs and standard deviations (SD) in the latanoprost- and travoprost-treated eyes at all time intervals during baseline

	Day 1				Day 2				Day 3			
Group	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00
Latanoprost												
Mean	14.2	14.0	12.8	12.5	16.4	15.2	13.8	15.8	12.3	12.6	10.3	11.5
SD*	3.7	3.7	3.6	3.8	4.4	4.0	3.4	3.0	2.3	3.0	2.9	3.0
Travoprost												
Mean	13.5	13.3	13.6	12.1	14.6	14.5	13.3	15.2	13.3	13.0	11.5	9.9
SD	5.4	3.5	2.9	2.3	3.6	3.3	3.1	3.8	2.3	3.0	4.3	2.6
Difference	0.7	0.7	−0.8	0.4	1.8	0.7	0.5	0.6	−1.0	−0.4	−1.2	1.6
P value†	0.73	0.66	0.59	0.77	0.33	0.67	0.73	0.70	0.34	0.76	0.47	0.21

*SD, standard deviation; †Student's *t*-test for independent samples.

Table 2. Mean IOPs and standard deviations (SD) in the latanoprost- and travoprost-treated eyes at all time intervals during the treatment period. Day 5 is not included because of imprecise tonometric readings

	Day 1				Day 2				Day 3				Day 4			
Group	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00
Latanoprost																
Mean	10.7	10.4	8.8	10.6	8.9	7.8	7.3	8.6	8.7	8.3	7.9	6.6	7.2	7.9	6.0	7.2
SD*	3.4	3.2	1.7	2.5	2.0	2.1	1.8	2.5	2.6	1.9	1.6	1.1	2.7	2.4	2.0	2.4
Travoprost																
Mean	9.1	9.5	10.2	9.9	8.8	8.5	7.6	7.8	7.5	7.9	6.8	6.2	5.3	7.8	7.1	8.0
SD	1.8	2.4	2.1	2.2	1.8	1.5	1.4	2.5	2.1	2.2	1.8	1.5	1.4	2.5	2.1	0.8
Difference	1.6	0.9	−1.4	0.7	0.1	−0.7	−0.3	0.8	1.2	0.4	1.1	0.4	1.9	0.1	1.1	0.8
P value†	0.20	0.49	0.12	0.52	0.91	0.40	0.68	0.48	0.31	0.67	0.17	0.25	0.06	0.93	0.25	0.34

*SD, standard deviation; †Student's *t*-test for independent samples.

Table 3. Mean IOPs and standard deviations (SD) in the latanoprost- and travoprost-treated eyes at all time intervals during the recovery period. Day 1 is not included because of imprecise tonometric readings

	Day 2				Day 3			
Group	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00
Latanoprost								
Mean	10.4	10.3	10.7	11.5	13.4	12.4	12.3	13.6
SD*	2.1	1.9	1.8	2.8	2.9	3.4	3.4	3.6
Travoprost								
Mean	10.4	9.2	10.1	10.6	12.2	11.2	10.8	12.2
SD	3.2	2.3	2.2	3.8	3.0	3.8	2.6	4.0
Difference	0.0	1.1	0.6	0.9	1.2	1.2	1.5	1.4
P value†	1.00	0.26	0.51	0.55	0.38	0.47	0.28	0.42

*SD, standard deviation; †Student's *t*-test for independent samples.

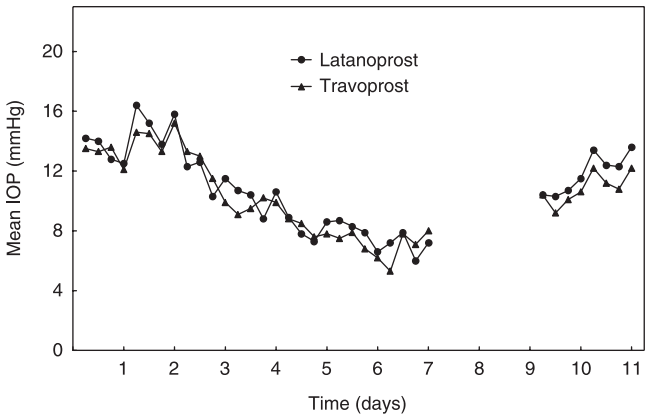

Figure 1. Mean IOPs in latanoprost- and travoprost-treated eyes throughout the study.

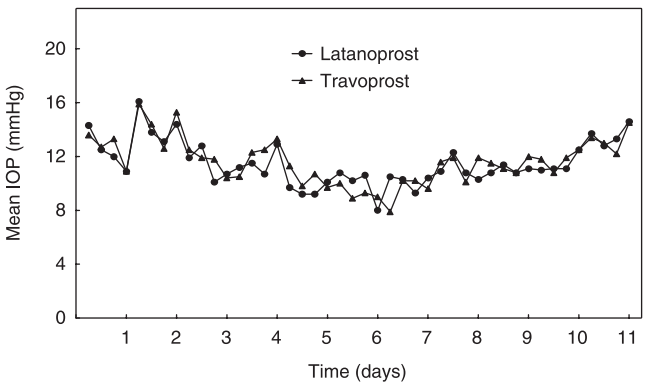

Figure 2. Mean IOPs of placebo-treated eyes in both groups throughout the study.

Figures 1 and 2 show the mean IOPs in the treated and contralateral eyes, respectively, during the entire experiment. Compared to baseline, there was a statistically significant decrease in IOP ($P \leq 0.03$, paired Student's *t*-test) in eyes treated with latanoprost and travoprost during the treatment period. On the fifth day of treatment, ocular hypotension was so severe that the IOP measurements became inconsistent. Such situation persisted up to the first day of the recovery period, so that the measurements became consistent once again on the second and third days of that period. During the third period (recovery), there was a gradual increase of IOP back to baseline values.

The maximum measurable ocular hypotensive effect caused by travoprost (mean IOP reduction of 44.6% from baseline) occurred on the fourth day of treatment at 8 AM. Regarding latanoprost, the maximum hypotensive effect occurred at 2 PM of the fourth day of treatment (mean IOP reduction of 40.3% from baseline). In both groups, the treated eyes showed consistent IOP reduction from baseline since the first day of treatment and returned to baseline values on the third day of the recovery period.

Table 4. Mean IOPs in the right eye (RE) (treated with latanoprost) and left eye (LE) (treated with placebo) during the treatment period at all time intervals. Day 5 is not included because of imprecise tonometric readings

	Day 1				Day 2				Day 3				Day 4			
Eye	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00
RE																
Mean	10.7	10.4	8.8	10.6	8.9	7.8	7.3	8.6	8.7	8.3	7.9	6.6	7.2	7.9	6.0	7.2
SD*	3.4	3.2	1.7	2.5	2.0	2.1	1.8	2.5	2.6	1.9	1.6	1.1	2.7	2.4	2.0	2.4
LE																
Mean	11.2	11.5	10.7	12.9	9.7	9.2	9.2	10.1	10.8	10.2	10.6	8.0	10.5	10.3	9.3	10.4
SD	3.8	3.4	2.4	2.9	2.7	2.6	2.1	2.9	3.5	2.3	2.2	1.9	3.1	2.3	2.3	2.5
Difference	0.5	1.1	1.9	2.3	0.8	1.4	1.9	1.5	2.1	1.9	2.7	1.4	3.3	2.4	3.3	3.2
P value†	0.45	0.14	< 0.01	< 0.01	0.09	0.03	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	0.01	< 0.01	< 0.01	0.01	< 0.01

*SD, standard deviation; †paired Student's *t*-test.

Table 5. Mean IOPs in the right eye (RE) (treated with travoprost) and left eye (LE) (treated with placebo) during the treatment period at all time intervals. Day 5 is not included because of imprecise tonometric readings

	Day 1				Day 2				Day 3				Day 4			
Eye	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00	8:00	10:00	14:00	20:00
RE																
Mean	9.1	9.5	10.2	9.9	8.8	8.5	7.6	7.8	7.5	7.9	6.8	6.2	5.3	7.8	7.1	8.0
SD*	1.8	2.4	2.1	2.2	1.8	1.5	1.4	2.5	2.1	2.2	1.8	1.5	1.4	2.5	2.1	0.8
LE																
Mean	11.2	11.5	10.7	12.9	9.7	9.2	9.2	10.1	10.8	10.2	10.6	8.0	10.5	10.3	9.3	10.4
SD	3.8	3.4	2.4	2.9	2.7	2.6	2.1	2.9	3.5	2.3	2.2	1.9	3.1	2.3	2.3	2.5
Difference	2.1	2.0	0.5	3.0	0.9	0.7	1.6	2.3	3.0	2.3	3.8	1.8	5.2	2.5	2.2	2.4
P value†	0.13	0.15	0.63	0.02	0.39	0.47	0.06	0.07	0.02	0.03	< 0.01	0.03	< 0.01	0.03	0.04	0.01

*SD, standard deviation; †paired Student's *t*-test.

The comparison between the mean IOPs of the treated and control eyes of group A (latanoprost) during the treatment period are displayed in Table 4. The mean IOPs of the latanoprost-treated eyes were significantly lower than the contralateral eyes in 13 of the 16 time intervals (81.2%). The comparison between the eyes treated with travoprost and those receiving placebo (group B) is shown in Table 5. Similarly to what happened with latanoprost, mean IOPs of the travoprost-treated eyes were significantly lower than the contralateral eyes in 9 of the 16 time intervals (56.2%).

Miosis and conjunctival hyperemia were identified at 10 AM in the treated eyes of both groups, during the entire treatment period. Blepharospasm was not observed, and a single transitory case of anterior chamber flare occurred in one latanoprost-treated eye during the first and second days of the treatment period.

DISCUSSION

In a study performed by Studer *et al*. (2000), latanoprost has been shown to be effective in lowering the IOP of normal dogs. Mean IOP reductions from baseline of 3.0 mmHg (approximately 25%) were observed. When comparing treated to control eyes, the mean IOP reduction was 1.9 mmHg, and the maximum hypotensive effect occurred on the fifth day of treatment. In our study, the mean IOP reduction from baseline varied between 2.75 and 7.45 mmHg (20–40%) for latanoprost, and between 2.95 and 7.85 mmHg (22–45%) for travoprost. When comparing treated to control eyes, the mean IOP reductions varied from 0.5 to 3.3 mmHg in the latanoprost group and between 0.5 and 5.2 mmHg in the travoprost group.[15]

Our findings indicate that both travoprost and latanoprost significantly reduced the IOP during the treatment period. However, there was no statistically significant difference between the mean IOP reduction of eyes treated with latanoprost and travoprost. During the third period (recovery), there was a gradual increase in IOP to baseline values. The fifth day of treatment and first day of recovery were characterized by imprecise tonometric readings caused by intense ocular hypotension.

Previous studies that evaluated prostaglandin effects on eyes of normal and glaucomatous dogs suggested that glaucomatous dogs seem to be more sensitive and demonstrate higher IOP reductions when compared to normotensive dogs.[18–20] Gelatt and Mackay (2001, 2004) reported a mean IOP reduction of up to 59% and 61% (single morning dose study; the last of 4 days of drug) in eyes of glaucomatous dogs treated with travoprost and latanoprost, respectively.[16,17]

Among the most frequent side effect observed with the use of latanoprost in human beings are conjunctival hyperemia, iris pigmentation,[21] eyelash changes, and superficial punctate

epithelial erosions.[22] Cases of iritis and anterior uveitis have also been described.[23] The side effects observed with travoprost are similar to those reported with latanoprost.[14,24]

In our study, side effects included conjunctival hyperemia and miosis with both drugs, and anterior segment inflammation in one eye treated with latanoprost. Studer *et al*. (2000) and Abrams (2002) have also described miosis as an important side effect caused by latanoprost in dogs.[15,25] Willis *et al*. (2002) observed miosis in normotensive and glaucomatous eyes of dogs and cats treated with latanoprost.[1] Studies have shown that the dog's isolated iris sphincter is more sensitive to $PGF_{2\alpha}$, which seems to stimulate iris contraction more than cholinergic neurotransmitters.[26,27] *In vitro* and *In vivo* studies have demonstrated that the iris sphincter of other species such as rabbits and nonhuman primates is not stimulated by any prostaglandin analog. The only exception is the cynomolgus monkey, whose iris sphincter reacts to $PGF_{2\alpha}$ in its pure form.[28]

We conclude that topical instillation of travoprost 0.004% and latanoprost 0.005% is similarly effective in reducing the IOP of normal dogs, and that miosis is the most frequent side effect observed during treatment. However, it is important to emphasize that the treatment period was short in our study, and that prolonged use of prostaglandin analogs may lead to the development of other side effects.

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