Effects of 0.005% latanoprost solution on intraocular pressure in healthy dogs and cats

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Objective—To evaluate effects of daily topical ocular administration of latanoprost solution on intraocular pressure (IOP) in healthy cats and dogs.

Animals—9 domestic shorthair cats and 14 dogs.

Procedure—Latanoprost solution (0.005%) was administered topically to 1 eye (treated) and vehicle to the other eye (control) of all animals once daily in the morning for 8 days. Intraocular pressure was measured twice daily for the 5 days preceding treatment, and IOP, pupillary diameter, conjunctival hyperemia, and blepharospasm were measured 0, 1, 6, and 12 hours after the first 4 treatments and 0 and 12 hours after the final 4 treatments. Measurements continued twice a day for 5 days after treatment was discontinued. Aqueous flare was measured once daily during and for 5 days after the treatment period.

Results—Intraocular pressure and pupillary diameter were significantly decreased in the treated eye, compared with the control eye. Mild conjunctival hyperemia was also detected, but severity did not differ significantly between eyes. Blepharospasm and aqueous flare were not detected in either eye. Intraocular pressure in cats was not significantly affected by treatment with latanoprost. However, pupillary diameter was significantly decreased in the treated eye, compared with the control eye. Conjunctival hyperemia, aqueous flare, and blepharospasm were not detected in either eye.

Conclusions and Clinical Relevance—Once-daily topical ocular administration of latanoprost solution (0.005%) reduced IOP in healthy dogs without inducing adverse effects but did not affect IOP in healthy cats. Latanoprost may be useful for treating glaucoma in dogs.

Latanoprost solution (0.003%) is a prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) analogue (13, 14-dihydro-17-phenyl-18, 19, 20-trinor-prostaglandin F<sub>2α</sub>-isopropyl ester; PhXXA4) approved for topical use to reduce intraocular pressure (IOP) in humans. There is evidence that it reduces pressure in humans by as much as 36% and is more effective administered once daily than 0.5% timol maleate administered twice daily. Moreover, latanoprost is effective over prolonged periods. It is well documented that prostaglandins (PG) reduce IOP in many species including cats, monkeys, rabbits, and dogs. However, concentrations of PG required to induce ocular hypotension were associated with induction of adverse effects such as ocular irritation and intraocular inflammation. Esterification of PG<sub>2α</sub> allows better penetration through the cornea; lower concentrations of this formulation were needed to produce a decrease in IOP.

The proposed mechanism of action of latanoprost is via an increase in uveoscleral outflow, although results of some studies suggest there is also an effect on conventional outflow. In cats, topical ocular administration of PG (eg, PGF<sub>2α</sub>, PGA<sub>2</sub>, and PGF<sub>2α</sub>) in various concentrations can reduce intraocular pressure, whereas latanoprost had little to no effect. Administration of drugs similar to latanoprost (ie, PGF<sub>2α</sub>–17-diphenyl and PGF<sub>2α</sub>–isopropyl ester) to healthy Beagles and Beagles with glaucoma reduces IOP. Prostaglandin F<sub>2α</sub>-isopropyl ester is a less selective PG analogue than latanoprost and stimulates a wider range of PG receptors, which results in ocular irritation and conjunctival hyperemia. These adverse effects have precluded its clinical use in humans. Reported adverse effects of latanoprost include mild conjunctival hyperemia in rabbits and humans and miosis in cats. Changes in iris pigmentation, hypertrichosis, and pigmentation of eyelashes have been detected in humans treated with latanoprost. Cystoid macular edema and anterior uveitis may develop after latanoprost use in humans but appear to affect primarily a subset of patients with a history of uveitis, previous ocular surgery, or prior cystoid macular edema.

The purpose of the study reported here was to determine whether a 0.005% latanoprost solution administered topically once daily for 8 days would reduce IOP in healthy dogs and cats. A secondary objective was to document development of adverse effects such as miosis, aqueous flare, blepharospasm, and conjunctival hyperemia associated with latanoprost administration.

Materials and Methods

Animals—Nine domestic shorthair cats (2 females, 7 males) between 2 and 8 years old and 14 female dogs (12 hound breeds, 1 Chow Chow, 1 mixed breed) between 4 and 13 years old were used in 2 separate experiments. Cats were evaluated initially, and the study protocol was repeated 2 months later, using dogs. All animals were part of nonocular research projects before enrollment in this study. All dogs and cats used were determined to have normal eyes on the basis of results of slit-lamp biomicroscopy, indirect ophthalm-
moscopy, Schirmer tear tests, and applanation tonometry. Animals were also determined to be healthy on the basis of physical examination.

Experimental protocol—Pretreatment measurements of IOP were obtained for both eyes at 8 AM and 8 PM for the 5 days preceding treatment (days 1 through 5). On day 6, 1 eye of each animal was assigned randomly to receive latanoprost (treated); vehicle (0.02% benzalkonium chloride, 0.5% monosodium phosphate monohydrate, 0.6% disodium hydrogen phosphate dihydrate, and 0.4% sodium chloride) was placed in the opposite eye (control). At 8 AM on each day of the 8-day treatment period (days 6 through 13), 30 µl of 0.005% latanoprost solution was administered topically to the treated eye, and 30 µl of vehicle was administered to the control eye.

Intraocular pressure, pupillary diameter, blepharospasm, and conjunctival hyperemia were measured 0, 1, 6, and 12 hours after treatment for the first 4 treatment days (days 6 through 9) and 0 and 12 hours after treatment for the last 4 treatment days (days 10 through 13); values determined 0 hours after treatment were considered baseline values for that day. On days 14 through 18, measurements were obtained at 8 AM and 8 PM. Aqueous flare was assessed only once each day (8 PM). The same investigator (MES) obtained all measurements.

Determination of IOP—Two tonometers were used for all IOP measurements. One instrument was used consistently throughout each experiment. Each instrument was calibrated and used in accordance with the manufacturer’s recommendations. Animals were restrained manually without sedation, and 1 drop of 0.5% proparacaine solution was placed in each eye before tonometry. Three consecutive readings with <5% variance were recorded and averaged to calculate 1 value for each eye at each time.

Determination of pupillary diameter, aqueous flare, blepharospasm, and conjunctival hyperemia—Pupillary diameter was measured in uniform illumination on the horizontal axis in the center of the pupil, using a millimeter ruler. Aqueous flare was graded with use of a slitlamp biomicroscope as 0 = none, 1 = slight, 2 = moderate, or 3 = severe. Blepharospasm was assessed as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Conjunctival hyperemia was evaluated, using a scale of 0 through 3. Standard photographs illustrating eyes with hyperemia of grade 0 (none), 1 (mild), 2 (moderate), or 3 = severe. Conjunctival hyperemia was detected in several eyes, but the number of treated eyes with conjunctival hyperemia was not significantly (P = 0.911) different from that of control eyes. A mild, dark, crusty exudate was detected on the medial canthal lid margins of both eyes in 3 of 9 cats during the last 7 days of the study. One cat developed transient mild superficial punctate epithelial opacities on days 5 through 10.

Statistical analyses—Changes in intraocular pressure and pupillary diameter were analyzed over the treatment period only, using the repeated-measures analysis of variance. Treatment effects were assessed by use of a mixed linear model. Sources of variation considered in the model were treatment, time, interaction, animal, and random. Treatment, time, and their interaction were considered fixed effects. Random effects were attributed to individual animal variation and random error for each observation. Scores for conjunctival hyperemia, aqueous flare, and blepharospasm were compared between treated and control eyes of each animal by use of the χ² test of independence for categorical variables. For all analyses, significance was set at P ≤ 0.05.

Results

In cats, once-daily topical application of 0.005% latanoprost solution induced no significant (P = 0.7186) change in IOP, mean (± SD) IOP in treated eyes during the 8-day treatment period was 13.9 ± 3.1 mm Hg and in control eyes was 14.0 ± 2.8 mm Hg. However, IOP decreased significantly (P < 0.001) over time in both treated and control eyes (Fig 1). Latanoprost had a significant (P < 0.001) effect on pupillary diameter in cats. All 9 cats developed extreme miosis in the treated eye within 1 hour of treatment (mean [± SD] pupillary diameter, 1.8 ± 0.64 mm). Diameter returned to the baseline value (7.3 ± 1.3 mm) by 24 hours. Pupillary diameter in the control eye was not affected by treatment. Aqueous flare and blepharospasm were not detected in either eye of any cat. Conjunctival hyperemia was detected in several eyes, but the number of treated eyes with conjunctival hyperemia was not significantly (P = 0.911) different from that of control eyes. A mild, dark, crusty exudate was detected on the medial canthal lid margins of both eyes in 3 of 9 cats during the last 7 days of the study. One cat developed transient mild superficial punctate epithelial opacities on days 5 through 10.

Mean IOP determined during the treatment period was significantly lower in the treated eyes of each dog, compared with control eyes (Fig 2). A significant (P < 0.001) decrease in IOP related to time was detected in both eyes over the entire study period (Fig 3). One dog had a mean decrease in IOP of 38.1%, compared with the mean baseline value before treatment, whereas another dog had a mean decrease of only 5.2%. During 1 measurement period, the decrease in IOP was as much as 56% for an individual dog. Mean IOP of treated eyes decreased by 3.0 mm Hg (24.5 ± 7.9%), compared with baseline values, during the treatment period. When IOP was compared between treated and control eyes during the treatment period, mean decrease for the treated group was 1.9 mm Hg (17.7 ± 6.2%). The mean maximum individual decrease was 2.9 mm Hg (33%), and minimum decrease was 1.1 mm Hg (10%). Maximum ocular hypotensive effect during the treatment period was detected on day 5 (5th treatment day), and the greatest reduction in IOP was detected 6 hours after treatment. Intraocular pressure in treated eyes approached pretreatment values 24 hours after the
selective agonist for PG receptors. Naturally occurring PG, including PGF \(_{2\alpha}\), without the adverse effect of ocular irritation. Latanoprost is a prodrug; it is biologically inactive when administered. Moreover, it is highly lipophilic, allowing for excellent corneal penetration. Latanoprost becomes trapped within the cornea, where it is completely hydrolyzed and released into the anterior chamber as the acid, or active, form. This allows sustained release of the active form of the drug from the cornea for approximately 24 hours; once-daily administration is recommended in humans.\(^{11,27}\)

In the present study, 0.005\% latanoprost solution applied once daily to the eyes of healthy dogs resulted in a decrease in IOP. However, latanoprost had no such effect in cats. Pupillary diameter was significantly reduced in the treated eyes of both species, compared with that of control eyes, a change that has been previously documented with topical administration of other FP receptor agonists.\(^{10,12a}\) Neither dogs nor cats developed evidence of anterior uveitis or ocular discomfort.

The mean reduction in IOP for dogs (3.0 mm Hg; 24.5 \(\pm\) 7.9\% less than pretreatment values) determined in the present study was comparable to results reported by Gum et al\(^1\) following administration of a similar PG analogue (PGF\(_{2\alpha}\)-isopropyl ester) to Beagles with and without glaucoma. Latanoprost has an additional ester group and phenyl ring that serves to increase FP-receptor selectivity and decrease induction of adverse effects (eg, ocular pain, conjunctival hyperemia). In our study, mean baseline IOP was low (11 mm Hg). It may be that the mean decrease in IOP attributable to latanoprost administration would have been greater had IOP been higher (ie, more similar to that in dogs with glaucoma) during the pretreatment period. In humans, reduction in IOP attributable to treatment with latanoprost was greatest in those people with the highest pretreatment IOP.\(^{27}\) The maximum effect of latanoprost on IOP of healthy dogs in our study was detected, on average, 6 hours after treatment.

A significant reduction in IOP was detected over time in control and treated eyes of dogs and cats. This may have been related to increased compliance of the animals as the study progressed, because the decrease was uniform in control and treated eyes before, during, and after treatment with latanoprost. In dogs, the magnitude of IOP reduction in treated eyes, compared with baseline IOP, was much greater than in control eyes, which supports a direct effect of the drug. However, systemic effects of latanoprost on the contralateral eye could not be disproved. There is evidence that drugs applied topically to 1 eye may also affect the untreated eye.\(^{39,46}\) This may be because of systemic uptake of the drug and a crossover effect to the contralateral eye.

There are several possibilities that may explain the lack of effect of latanoprost on IOP in cats, compared with that in dogs. The percentage of uveoscleral outflow in dogs is much greater than in cats (15\% vs 3\%, respectively).\(^{41}\) Latanoprost has been shown to reduce pressure via an increase in uveoscleral outflow\(^\text{13,16-18}\) and may have less effect in certain species if this pathway is not an important route for aqueous outflow. Another possible explanation for the difference in effect of latanoprost in dogs versus cats is the role of PG receptors. Naturally occurring PG, including

Discussion

Latanoprost is a PGF\(_{2\alpha}\) analogue and a highly selective agonist for receptors specific for PGF\(_{2\alpha}\) (FP receptors). It is designed to have the ocular hypoten-
PGF₂α, PGD₂, and PGE₂ are classified by the last letter in the abbreviation (D, E, F), which refers to the ring structure, and the number which refers to the number of unsaturated double bonds in the side-chains.³⁷ Prostaglycerin (PGI₂) and thromboxane A₂ (TXA₂) are also members of the PG family. Several different receptor subtypes mediate the effects of PG. Receptors with specific sensitivity to PGD₂, PGE₂, PGF₂α, PG₁α, or TXA₂ are classified as DP, EP, FP, IP, and TP respectively.³⁷ Receptors specific for PGF₂α (FP receptors) may be distributed variably within the eye so as to significantly impact the effects that PGF₂α and its analogues have in a given species or individual. Although there is evidence that PGF₂α decreases IOP in cats,³⁷ this effect appears to be caused by stimulation of receptors other than FP receptors alone.³⁷ Results of recent studies indicate that selective FP receptor agonists (eg, fluprostenol, AL-6221) stimulate extreme miosis but have no effect on IOP in cats.³⁷ In another study that compared PGF₂α and several analogues, the effect of PGF₂α on IOP was negatively correlated with FP-receptor stimulation.³⁷ Analogues such as latanoprost had less effect on pressure and more effect on pupillary constriction than PGF₂α. Using selective agonists and antagonists for EP and FP receptors, researchers have concluded that the IOP-lowering effect of PGF₂α analogues in cats is not moderated by FP receptors but by EP receptors.³⁷ This would explain why latanoprost, a selective FP agonist, did not affect IOP in cats in the present study.

Researchers have found that matrix metalloproteinase concentrations increase in vitro in response to PG (eg, PGF₂α, 17P-PGF₂α, latanoprost free acid) application to human ciliary smooth muscle cells. Degradation of the extracellular matrix surrounding the ciliary smooth muscle cells has been observed and is believed to facilitate increased flow of aqueous humor by decreasing resistance to outflow.³⁷ However, this protein-enzyme theory does not explain the rapid onset of action of PG analogues in reducing IOP in many species, including dogs.³⁷,¹⁰,¹³,¹⁵ It may be that relaxation of ciliary smooth muscle could account for the initial rapid decrease in IOP. Such an effect on ciliary muscle has been demonstrated in vitro, using ciliary muscle cultures³⁷ and fresh ciliary muscle tissue specimens.³⁷ The proposed mechanism of action is that PGF₂α and its analogues cause the release of endogenous PGE₂, which in turn activates the adenylyl cyclase system, resulting in relaxation of the ciliary muscle. The degree by which this mechanism is involved in reducing IOP needs to be further investigated.

Topical ocular administration of latanoprost to healthy dogs reduced IOP without causing adverse effects such as irritation or anterior uveitis. However, duration of treatment time was not adequate to determine whether once-daily administration would result in a decreased IOP over a prolonged period. During the first 2 days of treatment, IOP increased to baseline values by 24 hours after treatment. However, after 3 days of treatment, IOP remained consistently low in the treated eyes. This may have been because of a physiologic change within the eye in response to administration of latanoprost related to receptor stimulation or extracellular matrix changes in the ciliary body muscle. Intracocular pressures measured during the early treatment phase suggest that twice-daily administration may be required to initially control IOP. Failure of IOP to return to pretreatment values by the final day of the study may have been caused by a persistence of drug effect. However, IOP decreased over time in both control and treated eyes; this may be why IOP never returned to pretreatment values.

References


